IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **PUBLIC VERSION**

DECLARATION OF MARY B. MATTERER IN SUPPORT OF DEFENDANT IMPAX LABORATORIES, INC.'S MOTION TO COMPEL PRODUCTION OF DOCUMENTS IN RESPONSE TO DEFENDANT'S FOURTH SET OF REQUESTS FOR PRODUCTION (NOS. 125-131)

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Attorneys for IMPAX LABORATORIES, INC.

I, Mary B. Matterer, declare:

1. I am an attorney at the law firm of Morris James LLP, counsel of record for Defendant Impax Laboratories, Inc. ("Impax") in the above-referenced case. I have personal knowledge of the facts set forth in this Declaration.

2. I submit this Declaration in support of Defendant Impax Laboratories, Inc.'s Motion to Compel Production of Documents in Response to Defendant's Fourth Set of Requests for Production (Nos. 125-131).

3. A true and correct copy of United States Patent Number 6,274,171 is attached hereto as Exhibit A.

4. A true and correct copy of an article entitled "Companies Desperately Seek Antidepressant Breakthrough" published in Psychiatry News on June 2, 2006 Vol. 41 No. 11 Pg. 22 is attached hereto as Exhibit B.

5. A true and correct copy of an article entitled "Desvenlafaxine Succinate (DVS-233) Phase 3 Data Show Significant Improvement in Symptoms of Depression in Adult Patients Versus Placebo" published on the Medical News Today website on May 27, 2006 is attached hereto as Exhibit C.

6. A true and correct copy of Defendant Impax Laboratories, Inc.'s Fourth Set of Requests for Production (Nos. 125-131) is attached hereto as Exhibit D.

7. A true and correct copy of Wyeth's Supplemental Responses to Defendant Impax's Interrogatory Nos. 5, 6, 10, 11, 13, 17, 18, 19, 26 and 27 is attached hereto as Exhibit E.

8. A true and correct copy of an article entitled "Wyeth Receives Approvable Letter from FDA for Pristiq (Desvenlafaxine Succinate) for the Treatment of Major Depressive Disorder" published on the Medical News Today website on January 24, 2007 is attached hereto as Exhibit F.

9. A true and correct copy of Plaintiff's Responses and Objections to Impax's Fourth Request for Production of Documents and Things (Nos. 125-131) is attached hereto as Exhibit G.

10. A true and correct copy of a letter from Eric L. Lane, counsel to Impax, to Robert A. Pollock, counsel to Wyeth, dated April 4, 2007 is attached hereto as Exhibit H.

11. A true and correct copy of a letter from Robert A. Pollock, counsel to Wyeth, to Eric L. Lane, counsel to Impax dated April 3, 2007 is attached hereto as Exhibit I.

12. A true and correct copy of United States Patent Number 6,673,838 is attached hereto as Exhibit J.

13. A true and correct copy of the Wyeth 2004 package insert for Effexor XR is attached hereto as Exhibit K.

14. A true and correct copy of Defendant Impax Laboratories, Inc.'s First Amended Responses to Plaintiff's First Set of Interrogatories (Nos. 1-13) is attached hereto as Exhibit L.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Executed at Wilmington, Delaware on April 10, 2007.

Mary Matterer

MARY B. MATTERER (I.D. NO. 2696)

EXHIBIT A

US006274171B1

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,274,171 B1**
(45) **Date of Patent: Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

(75) Inventors: **Deborah M. Sherman**, Plattsburgh; **John C. Clark**, Peru, both of NY (US); **John U. Lamer**, St. Albans, VT (US); **Steven A. White**, Champlain, NY (US)

(73) Assignee: **American Home Products Corporation**, Madison, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/488,629**

(22) Filed: **Jan. 20, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/964,328, filed on Nov. 5, 1997, now abandoned, which is a continuation-in-part of application No. 08/821,137, filed on Mar. 20, 1997, now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25, 1996.

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/62

(52) **U.S. Cl.** **424/461**; 424/457; 424/458; 424/459; 514/781; 514/962

(58) **Field of Search** 424/495, 494, 424/461, 458, 459, 457, 456, 462

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,954,959		5/1976	Pedersen	424/21
4,138,475	*	2/1979	McAinsh et al.	424/19
4,369,172		1/1983	Schor et al.	424/19
4,389,393		6/1983	Schor et al.	424/19
4,535,186		8/1985	Husbands et al.	564/336
4,966,768		10/1990	Michelucci et al.	424/468
5,506,270		4/1996	Upton et al.	514/730
5,552,429	*	9/1996	Wong et al.	514/415

FOREIGN PATENT DOCUMENTS

0654264	11/1994	(EP) .
0667150	1/1995	(EP) .
0797991	10/1997	(EP) .
9427589	12/1994	(WO) .
9737640	10/1997	(WO) .

* cited by examiner

Primary Examiner—James M. Spear
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(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

25 Claims, No Drawings

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997 abandoned, which is a continuation-in-part of Application Ser. No. 08/821,137, filed Mar. 20, 1997 abandoned, which, in turn, claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug s component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine Is hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally,

hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about I percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2–5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50–55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1–4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable

capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\%\ \text{Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 × 75 mg (ER)capsules (q 24 hr)	1 × 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hours intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4. hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As

quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at −20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm×4.6 mm, 5 μ; column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by is weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation of venlafaxine hydrochloride according to claim 1 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 1 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

12. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose, and about 62% by weight of microcrystalline cellulose.

13. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. An extended release formulation according to claim 1 wherein the film coating comprises 6–8% by weight of total weight.

15. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. An extended release formulation according to claim 1 wherein the film coating composition is comprised of ethyl cellulose having a 44.0–51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

17. An extended release formulation according to claim 1 wherein the film coating composition is comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0–51% content of ethoxy groups and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

18. An extended release formulation according to claim 1 wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0–51% and a viscosity of 50% cps for a 5% aqueous solution, and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose coated with a quantity of a mixture comprised of 85% ethyl cellulose and 15% hydroxypropylmethylcellulose sufficient to give coated spheroids having a dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.:

Time	Average % Venlafaxine HCl Released
2	<30
4	30–55
8	55–80
12	65–90
24	>80.

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides

a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

21. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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EXHIBIT B

Psychiatr News June 2, 2006
Volume 41, Number 11, page 22

Clinical & Research News

Companies Desperately Seek Antidepressant Breakthrough

Jim Rosack

The second installment in an exclusive *Psychiatric News* series on psychotropic drugs in the developmental pipeline takes a look at the future of medication therapy for people with depressive and anxiety disorders. While no innovative medications will be released in the short term, new treatment options are expected in the long term.

For those with depressive disorders, the reality of medication therapy alone is all too bleak. Research has shown that only about one-third of patients achieve symptomatic remission with the first antidepressant medication they try.

Even after trying two antidepressants, patients with depression still have only about a 50 percent chance of achieving remission *(Psychiatric News*, January 20, April 21). Clinical trial and case-study data suggest the overall odds of remission are roughly the same for those with anxiety disorders. However, for those with obsessive/compulsive disorder or panic disorder, success with medication therapy can be especially difficult to achieve.

Clearly, new treatment options are needed for patients with depressive or anxiety disorders. During 2004, the most recent year for which statistics are available, an estimated 21 million people were diagnosed with major depressive disorder in the United States, Western Europe, and Japan (the world's top three pharmaceutical markets), yet only half of all patients receive any treatment.

The prospect of large populations of patients with unmet medication needs is certainly ample reason for the world's research-oriented pharmaceutical companies to search for new drugs to fill the treatment gap. Treating depression and anxiety is big business (see box on facing page). Indeed, a large pool of pharmaceutical companies is working hard to bring new medications to the market.

Through an extensive review of documents from the Food and Drug Administration, pharmaceutical companies, industry analysts, and other sources, as well as interviews with numerous experts, *Psychiatric News* has identified nearly 60 medications in development to treat depressive and anxiety disorders. Many of those medications are being studied for both depression and anxiety, following the obvious success of the selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) in treating both. However, at least 20 drugs in development are being studied only as antidepressants, and about 10 are in development only as anxiolytics.

The drugs under development to treat depression and anxiety, however, are only part of the pharmaceutical industry's overall effort in the psychiatric market. According to a report released last month by the Pharmaceutical Research and Manufacturers of America, a professional association that represents most of the larger, research-oriented pharmaceutical companies, the industry is developing 197 medications to treat mental illness. Not surprisingly, the largest number—57—are targeted at Alzheimer's disease and other dementias. However, coming in a close second and third are medications for depression, at 44, and anxiety, at 39.

Meds Trickle From Crowded Pipeline

Of the dozens of medications in development to treat anxiety and/or depression, only a few are in the mid- to late stages of development (phase 2 or phase 3 clinical trials). In these stages, medications are being tested in large-scale human clinical trials. Phase 2 involves testing a drug in 100 to 500 patients to evaluate the drug's effectiveness and identify side effects. Phase 3 involves testing a drug in 1,000 to 5,000 patients to confirm the drug's effectiveness and monitor adverse drug reactions over longer periods of time. By the time a drug reaches phase 3, it has already undergone years of scrutiny in the laboratory, animal trials, and smaller human trials and has the best chance of reaching pharmacy shelves within the next 18 months to three years.

Currently, one new medication for depression has completed all clinical testing and has been submitted to the U.S. Food and Drug Administration (FDA), and possibly other regulatory bodies across the globe, for approval. Two medications already marketed for other indications are awaiting FDA approval for the treatment of anxiety disorders. The phase 3 pipeline holds several drugs indicated for depression and/or anxiety disorders (several drugs are under study for both). These drugs could reach pharmacy shelves by 2008. Phase 2 studies are under way for nearly 20 other putative antidepressants/anxiolytics, as well as several drugs targeted only for anxiety disorders.

"The majority of drugs in late-stage development for depression are similar to the drugs that are already on the market, in that they target the monoamines: serotonin, norepinephrine, or dopamine," Anathea Waitekus, M.P.H., an analyst with Decision Resources, told *Psychiatric News*.

The drugs in the pipeline attracting the most interest, however, are the "triple re-uptake inhibitors (TRIs)," Waitekus and several other analysts told *Psychiatric News*. As many as 15 TRIs have been in the pipeline over the last five to 10 years; however, "the ability of a number of these compounds to reach the market is questionable," added Emma Travis, a senior CNS sector analyst with Datamonitor.

"The last five years has seen a large number of products in development for depression fall from the pipeline," Travis continued, "highlighting the difficulty in moving compounds through late-stage development and the complexity of demonstrating clear advances in efficacy and side effect [profiles] compared to currently marketed products."

While the depression pipeline "contains some interesting compounds, including [neurokinin] receptor

antagonists and the triple reuptake inhibitors," Travis said, in the anxiety drug market, "growth has traditionally come from the SSRIs' and SNRIs' gaining additional indications for anxiety. Not surprisingly then, the current late-stage pipeline is made up of a number of existing CNS market players seeking approvals for secondary indications in anxiety." The anxiety pipeline, she said, contains "only a few novel compounds."

Immediate Future and Beyond

Based on information compiled by *Psychiatric News,* the following compounds are deemed by industry analysts to be the most likely to reach drugstores over the next two to three years (see table). Analysts stressed the highly competitive nature of the depression market, noting that "most pharmaceutical companies chasing new antidepressants release as few details as possible."

- The drug closest to reaching pharmacy shelves for major depressive disorder (MDD) is GlaxoSmithKline's new SNRI, desvenlafaxine. The drug is the active metabolite of venlafaxine (GSK's Effexor/Effexor XR) and was developed as a replacement for the older drug, which loses patent protection in 2008. GSK submitted an NDA for desvenlafaxine extended release last December, and an initial FDA decision is expected this summer.

Desvenlafaxine is said by those familiar with the clinical trials data to retain the efficacy of its predecessor and may possibly be more efficacious. In addition, the drug appears to boast a more tolerable side-effect profile than its predecessor. Supplemental NDAs for desvenlafaxine for the treatment of anxiety disorders are likely to follow over the next few years, analysts agreed.

- The fate of gepirone extended release, a direct-acting serotonin partial agonist intended to treat MDD, is now in the hands of the small, privately held Fabre-Kramer Pharmaceuticals. Organon originally submitted an NDA for gepirone to the FDA in 2001. After much back and forth between the agency and Organon over the adequacy of the dataset submitted, the FDA finally deemed the application "not approvable" in June 2004. Organon subsequently announced it would not continue to pursue the drug's approval and in June 2005 sold all rights to the drug to Fabre-Kramer. Fabre-Kramer had been expected to submit a revised NDA to the FDA earlier this spring; however, this submission could not be confirmed.
- Two medications already on the market are awaiting FDA approval for new indications to treat anxiety disorders. The FDA's initial review of Eli Lilly and Co.'s duloxetine (Cymbalta) for generalized anxiety disorder (GAD) is due by November. Cymbalta, an SNRI that debuted in late 2004, is approved for the treatment of MDD and diabetic peripheral neuropathic pain.

In March 2005 the FDA deemed Forest Laboratories' escitalopram (Lexapro) "not approvable" for the treatment of panic disorder and social anxiety disorder. At that time, the company said publicly that the agency expressed concerns about subsets of data within the two phase 3 clinical trials submitted in support of the applications. Both applications, filed by Forest in 2004, remain active at the FDA, analysts noted, indicating to them the company's intention to continue to work with regulators to gain

final approval. Lexapro is approved for use in GAD and MDD.

In 2003 Pfizer submitted a new drug application (NDA) for pregabalin (Lyrica) for the treatment of GAD; however, in September 2004 the FDA deemed that application "not approvable." (The drug did gain approval as a treatment for neuropathic pain and as an adjunct treatment for partial seizures.) Pregabalin gained European Union approval for GAD in March; at the same time, an additional phase 3 clinical trial was initiated in the United States aimed at addressing the FDA's questions and concerns. Data from that trial, analysts agreed, could possibly be submitted to the FDA as early as the end of 2007.

While all of these drugs are under regulatory review, *Psychiatric News* made multiple attempts over the last three months to clarify their status in the pipeline. Due to regulations governing the confidentiality of pharmaceutical manufacturers' proprietary information, the FDA does not comment publicly on the status of drug applications, even to confirm receipt of a submission. Moreover, most of the companies contacted for this article did not respond to requests for comment. However, both Lilly and Pfizer Inc., through their spokespersons, expressly declined to speak with *Psychiatric News* regarding any aspect of their products in development.

Phase 3 Holds New Promise

The phase 3 pipeline boasts several novel drugs to treat both depressive and anxiety disorders. Clinicians involved in clinical trials for these putative medications, analysts said, seem most excited about the advent of the triple reuptake inhibitors, which target all three of the brain's mono-amines (serotonin, norepinephrine, and dopamine).

- At least one TRI, Merck and Co.'s DOV 216303, is in phase 3 trials and could reach the market by 2010. GSK's NS 2359 could also launch about the same time. DOV Pharmaceuticals (which licensed DOV 216303 to Merck) and Sepracor also have TRIs in earlier stages of development.

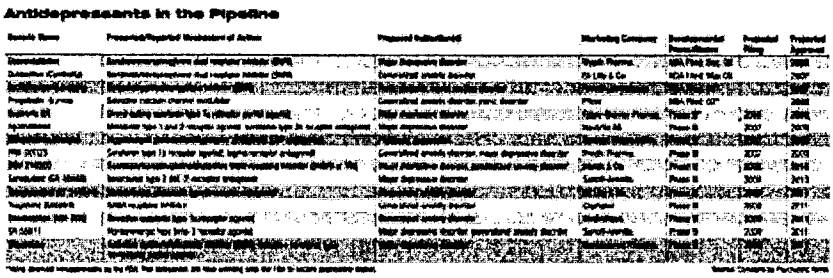
TRIs "will be the next blockbusters in major depression," noted Natalie Taylor, Ph.D., an analyst at Decision Resources and author of a January report reviewing the major depression drug market. Sales of TRIs could reach $1.5 billion to $2.0 billion per product each year as early as the second or third year after market introduction.

Because of their new mechanism of action, TRIs "are expected to offer a clinically significant difference in efficacy and in tolerability," Taylor noted in her report. The drugs are believed to offer advantages in efficacy over existing SSRIs and SNRIs, addressing a broader array of symptoms and having a faster onset of action. TRIs are also expected to have fewer side effects, in particular, a lack of drug-associated weight gain and sexual dysfunction, common with many of the currently available medications.

"There are also drug developers looking farther into the future, looking past the monoamine system to see truly novel mechanisms of action," Decision Resources' Waitekus told *Psychiatric News*.

- Novartis is progressing through phase 3 with agomelatine, a drug developed by French

pharmaceutical company Servier. Agomelatine acts as an agonist at melatonin type 1 and type 2 receptors while antagonizing serotonin type 2C receptors. In clinical trials the drug has been especially free of such side effects as weight gain, sexual dysfunction, and gastrointestinal problems. In addition, because it interacts with melatonin receptors, the drug has a favorable effect on both sleep and daytime alertness. Novartis, which acquired the drug in March, declined at thattime to say when it plans to file an NDA for agomelatine.



Specific Pathways Being Targeted

While many analysts cautioned that the next few years will largely bring new drugs that are similar to those already on the market, they also expressed optimism that advancing technologies—including new methods of imaging diseased nervous systems and elucidating the biochemical and anatomical pathways underlying psychiatric disorders—will lead to new medications with highly specific targets, including genes and regulating proteins.

Several companies are developing a new class of antidepressant, known as anti-tachykinin or tachykinin-receptor modulator" drugs. There are three tachykinin receptors in humans: the neurokinin-1 (NK-1) receptor, which is found throughout the central and peripheral nervous system and preferentially binds the peptide substance-P; the neurokinin-2 (NK-2) receptor, which is found primarily in the peripheral nervous system and preferentially binds the peptide neurokinin-A; and the neurokinin-3 (NK-3) receptor, which is found in the CNS and binds to the peptide neurokinin-B.

Compounds that bind to and block NK-1 (NK-1 antagonists) may be useful to treat nausea, vomiting, and depression. Compounds that block NK-2 appear to be useful as anxiolytics, while those that block NK-3 have been studied to treat depression, bipolar disorder, and schizophrenia, as well as cognitive deficits associated with Parkinson's disease and the dementias.

Sanofi-Aventis is proceeding with phase 3 clinical trials of saredutant, an NK-2 antagonist, for depression. Phase 2 data are said to be "very promising," and the drug is the farthest along of any of the anti-tachykinins in the pipeline. Roche Pharmceuticals and GSK also have anti-tachykinin antidepressants/anxiolytics in their pipelines.

Another novel target being pursued for the treatment of depression and anxiety (as well as other indications) is corticotrophin releasing factor (CRF). Numerous CRF antagonists, also known as glucocorticoid receptor antagonists, are in development, with Corcept Therapeutics' mifepristone (Corlux) farthest along in the pipeline. These drugs attempt to reduce the flood of cortisol released by both physical and emotional stress. Researchers theorize that the release of large amounts of cortisol

over time leads to neuronal damage and is possibly responsible for some of the structural changes noted in the brains of some patients with severe mental illnesses.

Other companies are moving other novel antidepressants and anxiolytics through the pipeline, including highly specific serotonin modulators, selective noradrenergic antagonists, and compounds that interact with numerous other receptor complexes thought to be involved in psychiatric disorders.

Nonetheless, Kate George, an analyst at IMS Health and editor of the *IMS LifeCycle R&D Report,* cautioned that "even if future research permits the identification of specific receptor regions and receptor subtypes involved in depression," the development of drugs with more specific mechanisms of action and fewer side effects may not be appreciably more effective than current medications.

"Depression," George wrote in a February 2006 *LifeCycle R&D Report,* "is a genetically complex disorder... and behavior is complex and multifactorial." That complexity, she added, "combined with the infancy of these biotech programs, means that a ground-breaking pharmacologic therapy or use of tailored therapy for depression is a long way off—and may never be possible at all." ■

EXHIBIT C

Medical News TODAY www.medicalnewstoday.com

Desvenlafaxine Succinate (DVS-233) Phase 3 Data Show Significant Improvement In Symptoms Of Depression In Adult Patients Versus Placebo

27 May 2006 Click to Print

Wyeth Pharmaceuticals, a division of Wyeth (NYSE: WYE), this week presented for the first time phase 3 data and results from other studies concerning its investigational drug for major depressive disorder (MDD), desvenlafaxine succinate (DVS-233), a novel serotonin-norepinephrine reuptake inhibitor (SNRI) at the 2006 American Psychiatric Association Annual Meeting in Toronto.

Overall, the phase 3 data results showed desvenlafaxine succinate significantly improved depressive symptoms in adult patients compared to placebo. In a separate study investigating QTc prolongation involving healthy adult female subjects, desvenlafaxine succinate 200 mg and 600 mg doses did not affect the QT interval at the study's primary endpoint at eight hours post dose. Studying a drug's effect on the QT interval is one of many methods used to help determine a drug's overall safety profile.

Wyeth Research discovered and developed desvenlafaxine succinate. In December 2005, Wyeth submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for desvenlafaxine succinate for the treatment of MDD.

"The phase 3 data showed that desvenlafaxine succinate can help improve symptoms in adult patients suffering with depression," says Nicholas A. DeMartinis, M.D., Assistant Professor and Associate Director of Clinical Operations of the Neuropsychopharmacology Treatment Research and Training Center at the University of Connecticut Health Center and principal investigator of the clinical trial presented in the scientific session.

"Because a substantial number of patients with depression do not respond to current antidepressant treatments, it is important that new treatments continue to be developed to provide patients and physicians with additional treatment options," Dr. DeMartinis adds.

"Wyeth is pleased to be able to report these promising findings that have the potential to add value to the management and treatment of major depressive disorder," says Philip Ninan, Vice President, Neuroscience, Global Medical Affairs. "As a leader in neuroscience, Wyeth is committed to its continuing development of medications that help address the unmet needs of people living with mental illness."

Abstract: Efficacy and Safety of Desvenlafaxine Succinate in the Treatment of Major Depressive Disorder.

The results of the first study presented, a phase 3, multicenter, randomized, double-blind clinical trial of desvenlafaxine succinate in 461 adult patients with MDD, showed significant reduction in Hamilton Depression Rating Scale (HAM-D17) scores for the desvenlafaxine succinate 100 mg ($p = .0038$) and 400 mg ($p=0.0023$) dose groups versus the placebo group. For the 200 mg dose group, reduction in the HAM-D17 trended towards significance ($p=0.0764$). All desvenlafaxine succinate dose groups showed significant improvement on the Clinical Global Impression-Improvement (CGI-I) scale, a secondary efficacy measure, versus placebo ($p< 0.05$). Additionally, the 100 mg desvenlafaxine succinate group demonstrated significant improvement versus placebo in depression-related pain scores utilizing the Visual Analog Scale- Pain Intensity (VAS-PI) scale ($p=0.002$).

Abstract: Randomized, Double-Blind, Placebo-Controlled Study of Desvenlafaxine Succinate in Major Depressive Disorder

The results of a second phase 3, randomized, double-blind, placebo- controlled study of desvenlafaxine succinate were also presented at the APA annual meeting. In this second study, 375

adult patients with major depressive disorder were randomized to receive desvenlafaxine succinate once- daily doses of 200 mg, 400mg, or placebo. Adjusted mean change from baseline in HAM-D17 total score, the primary efficacy measure, was significantly greater for the desvenlafaxine succinate 200 mg (p=0.002) and 400 mg (p=0.008) dose groups versus placebo. In addition, overall VAS-PI scores for the desvenlafaxine succinate 200 mg group were significantly better than placebo (p=.002). There was a trend toward significance for the desvenlafaxine succinate 400 mg group (p=0.053).

In the two phase 3 desvenlafaxine succinate clinical trials presented at the APA, adverse events, including nausea and increased blood pressure, were generally consistent with the SNRI class. The incidence of nausea was greatest during week 1 of treatment and decreased dramatically afterwards to rates that remained low for the remainder of the study. The most common treatment emergent adverse events (i.e., those reported by at least 10 percent of desvenlafaxine succinate patients, and twice the rate of patients on placebo) were abdominal pain, asthenia, anorexia, constipation, dry mouth, nausea, vomiting, dizziness, insomnia, nervousness, somnolence, sweating, tremor, vertigo, and abnormal ejaculation. Most of these adverse events in both studies were mild or moderate in severity.

Abstract: Double-blind, Placebo- and Moxifloxacin-controlled Crossover Study of the Effects of Desvenlafaxine Succinate on QT Interval in Healthy Adult Female Subjects

To help determine whether desvenlafaxine succinate had effects on the QT interval, a randomized, double-blind study of 71 healthy adult women (ages 18 to 55) was conducted. In the study, desvenlafaxine succinate 200 mg and 600 mg dose groups did not affect the QT interval at the primary endpoint at eight hours post dose. Because many drugs are known to be associated with a potential to prolong QT interval, the FDA developed guidance recommending that all manufacturers conduct a QT interval study to help determine whether any new agent may potentially prolong the QT/QTc interval, one of many important measures of cardiovascular safety.

Abstract: Desvenlafaxine: Preclinical Evidence for Serotonin and Norepinephrine Reuptake Inhibition, Antidepressant, and Antinociceptive Activity

According to research also presented during the APA, desvenlafaxine succinate exhibited activity in preclinical models of depression and anxiety.

Facts About Depression

Following are facts that substantiate the significant unmet patient need for additional antidepressant treatment options and the enormous societal impact of depression.

Depression is the most common serious mental disorder worldwide.

-- Depression affects approximately 121 million people worldwide and is the fourth leading cause of disability and premature death.

-- The World Health Organization projects that by the year 2020, depressive disorders will become the second-leading cause of disability worldwide.

-- Depression is one of the most prevalent mental health conditions in the United States, affecting approximately 14.8 million American adults each year.

-- Women suffer from depression twice as often as men.

More treatment options are needed.

-- Researchers estimate that approximately 50 to 60 percent of patients suffering from depression respond to antidepressant therapy, leaving a large percentage of patients with unresolved depression.

-- Patients who experience one episode of depression have a 50 to 60 percent chance that it will recur.

Depression is both a physical and mental illness.

The most common symptoms include:

-- Feelings of hopelessness and sadness

-- Crying, thoughts of death or suicide

-- Lack of motivation

-- Changes in appetite and weight

-- Feelings of guilt for no apparent reason

-- Changes in sleep patterns

-- Loss of interest in activities or friends

-- Trouble concentrating

-- Headache

-- Pains in the chest, back, joints and muscles

-- Gastrointestinal complaints

Wyeth Is Committed to Neuroscience Research and Development As a leader in neuroscience, Wyeth's discovery and development of desvenlafaxine succinate demonstrates its commitment to developing pharmaceutical products to help address the unmet needs of patients living with mental illness. In addition to the investigational compound desvenlafaxine succinate for major depressive disorder, the Company also has active research programs in mental health areas, including bipolar disorder, schizophrenia, and Alzheimer's disease.

About Antidepressants

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders. Anyone considering the use of any antidepressant in a child or adolescent must balance the risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

About Wyeth Pharmaceuticals

Wyeth Pharmaceuticals, a division of Wyeth, has leading products in the areas of women's health care, cardiovascular disease, central nervous system, inflammation, transplantation, hemophilia, oncology, vaccines and nutritional products. Wyeth is one of the world's largest research-driven pharmaceutical and health care products companies. It is a leader in the discovery, development, manufacturing, and marketing of pharmaceuticals, vaccines, biotechnology products and nonprescription medicines that improve the quality of life for people worldwide. The Company's major divisions include Wyeth Pharmaceuticals, Wyeth Consumer Healthcare and Fort Dodge Animal Health.

The statements in this press release that are not historical facts are forward-looking statements based on current expectations of future events and are subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. These risks and uncertainties include risks associated with the inherent uncertainty of the timing and success of product research, development and commercialization (including with respect to our pipeline products), drug pricing and payment for our products by government and third party-payors, manufacturing, data generated on the safety and efficacy of our products, economic conditions including interest and currency exchange rate fluctuations, changes in generally accepted accounting principles, the impact of competitive or generic products, trade buying patterns, global business operations, product liability and other types of litigation, the impact of legislation and regulatory compliance, intellectual property rights, strategic relationships with third parties, environmental

liabilities, and other risks and uncertainties, including those detailed from time to time in our periodic reports filed with the Securities and Exchange Commission, including our current reports on Form 8-K, quarterly reports on Form 10-Q and annual report on Form 10-K, particularly the discussion under the caption "Item 1A, Risk Factors." We assume no obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

Wyeth

http://www.wyeth.com

Article URL: http://www.medicalnewstoday.com/medicalnews.php?newsid=44128

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	)	Civil Action No.: 06-222 JJF

DEFENDANT IMPAX LABORATORIES, INC.'S
FOURTH SET OF REQUESTS FOR PRODUCTION (NOS. 125-131)

Pursuant to Federal Rule of Civil Procedure 34, Defendant Impax Laboratories, Inc. ("Impax") by its counsel, directs the following Requests for Production to Plaintiff Wyeth to produce all documents and things requested herein at the offices of Heller Ehrman LLP, 333 Bush Street, San Francisco, California, 94104, within 30 days of the date of service hereof. Impax reserves the right to serve additional discovery.

DEFINITIONS

When used in the following requests for production, the following definitions apply:

1. "WYETH" or "PLAINTIFF" means Plaintiff Wyeth and that company as it was previously named and any related companies, parents, divisions, or subsidiaries, past or present, located in the U.S. or abroad, and the past or present directors, officers, employees, agents, representatives or attorneys thereof.

2. "IMPAX" or "DEFENDANT" means Defendant IMPAX Laboratories, Inc. and its past or present directors, officers, employees, agents, representatives or attorneys known to WYETH.

3. "CONCERNING" means referring to, relating to, regarding, reflecting, associated with, comprising, constituting, containing, demonstrating, describing,

discussing, evidencing, evincing, indicating, on the subject of, on the topic of, showing, or prepared in connection with the stated matter.

4. "DATE" means the exact day, month, and year, if so ascertainable, or if not, the best approximation (including relationship to other events).

5. "DOCUMENT" or "DOCUMENTS" means all written, printed, typed, electronically produced, electronically stored, photostatic, photographed, recorded, or otherwise reproduced communications or records of every kind and description, whether comprised of letters, words, pictures, sounds, symbols, or combinations thereof. DOCUMENTS include originals as well as drafts, copies, marked-up copies, non-identical duplicates, and computer files, including backup or archival copies.

6. "THING" or "THINGS" means any tangible item, including without limitation models, prototypes, research models or samples, and samples of any device or apparatus, or product.

7. "PERSON" means any natural person, firm, association, organization, partnership, business, trust, corporation, or public entity.

8. "IDENTIFY" used with respect to a DOCUMENT means to provide: the kind of DOCUMENT (e.g., letter, memo, etc.); the title or name by which the DOCUMENT is referred to; the DATE of the DOCUMENT; the identity of its author or the PERSON creating the DOCUMENT; the identity of each PERSON to whom the DOCUMENT was addressed, sent, or copied; the present location of the original and all copies thereof; the name of the custodian of the DOCUMENT; and a general description of the subject matter.

9. "IDENTIFY" used with respect to a PERSON, means to state:

(a) His, her, or its full name and all known business or other addresses and telephone numbers;

(b) If a natural PERSON, his or her last known residence address and telephone number; and

(c) Such PERSON's relationship to WYETH.

10. "IDENTIFY" used in reference to an act, instance, transaction, occasion, oral discussion, conversation, communication, or event, means to state the DATE upon which and the location at which it occurred, the identity of each PERSON who participated therein or who was present when it occurred, its substance (i.e. what was said and by whom and/or what transpired) and the identity of each DOCUMENT, which, in whole or in part, was the subject of the act or in which it is manifested, referred to or expressed.

11. "PTO" means the United States Patent and Trademark Office.

12. "FDA" means the United States Food and Drug Administration.

13. "NDA" means New Drug Application.

14. "ANDA" means Abbreviated New Drug Application.

15. "INDA" means Investigational New Drug Application.

16. "ORANGE BOOK" means the FDA publication entitled, *Approved Drug Products with Therapeutic Equivalence Evaluations*.

17. "IMPAX'S VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULE" means those pharmaceutical products that are the subject of ANDA No. 78-057.

18. "VENLAFAXINE" means the compound 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol commonly known as venlafaxine, as well as all compositions, formulations, and preparations containing venlafaxine, including without limitation VENLAFAXINE and other pharmaceutically acceptable salts of venlafaxine.

19. "DESVENLAFAXINE" means the compound 4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl] phenol, commonly known as desmethylvenlafaxine as well as all compositions, formulations, and preparations containing venlafaxine, including without limitation DESVENLAFAXINE and other pharmaceutically acceptable salts of desmethylvenlafaxine.

20. "EFFEXOR" means the VENLAFAXINE product sold by WYETH as

Effexor®.

21. "EFFEXOR XR" means the VENLAFAXINE product sold by WYETH as Effexor® XR.

22. "PATENTS IN SUIT" means U.S. Patent No. 6,274,171 B1, U.S. Patent No. 6,403,120 B1, U.S. Patent No. 6,419,958 B2, and any other patent asserted by WYETH as infringed by IMPAX in the above-captioned action, individually or collectively.

23. "NAMED INVENTORS" means Deborah M. Sherman, John C. Clark, John U. Lamer, Steven A. White, and any other person listed as an inventor for the PATENTS IN SUIT, individually or collectively.

24. For the purposes of these requests for production only, "EXTENDED RELEASE FORMULATION" means a formulation which releases the active ingredient at a slower rate than the immediate release formulation of the active ingredient such that the desired dosing frequency is or would be less than that for the immediate release formulation.

25. "WYETH'S REPLY" means Plaintiff Wyeth's Reply to First Amended Counterclaims of Defendant Impax Laboratories, Inc. filed by WYETH in the above-captioned action on August 30, 2006, and any amendments thereto.

26. "ALZA" means Alza Corporation, and its past or present directors, officers, employees, agents, representatives or attorneys known to WYETH.

INSTRUCTIONS

A. Each request below extends to any DOCUMENTS and THINGS in the possession, custody or control of WYETH. A DOCUMENT or THING is deemed to be in your possession, custody or control, if it is in your physical custody, or if it is in the physical custody of any other PERSON and you (a) own such DOCUMENTS in whole or in part; (b) have a right by contract, statute or otherwise to use, inspect, examine or copy such DOCUMENTS on any terms; (c) have an understanding, express or implied, that you

may use, inspect, examine or copy such DOCUMENTS on any terms; or (d) have, as a practical matter, been able to use, inspect, examine or copy such DOCUMENTS when you have sought to do so. Such DOCUMENTS or THINGS shall include, without limitation, DOCUMENTS that are in the custody of your attorneys or other agents.

B. In construing these requests, the plural shall include the singular and the singular shall include the plural; a masculine, feminine, or neuter term shall include all other genders; the terms "or," "and," "and/or," and "including" shall be construed conjunctively and inclusively rather than exclusively so as to bring within the scope of the request that which otherwise might be construed as being outside the scope of said request; and the terms "all" and "any" shall be interpreted inclusively so as to mean both "all" and "any" whenever either term is used.

C. Unless otherwise stated, the time period covered by this notice is up to and including the DATE on which the DOCUMENTS are produced.

D. Pursuant to Federal Rule of Civil Procedure 26(e), these requests for production of DOCUMENTS and THINGS are deemed continuing to the fullest extent permissible and to apply to all DOCUMENTS and THINGS that you subsequently create, develop, discover, or receive.

E. If you cannot respond to any request in full, you should respond to the fullest extent possible, explain why you cannot respond to the remainder, and describe the nature of the DOCUMENTS or THINGS that you cannot furnish.

F. Pursuant to Federal Rule of Civil Procedure 26(b)(5), it is not intended that this notice require the disclosure of any DOCUMENTS or THINGS that are privileged where such privilege has not been waived. For any DOCUMENTS and THINGS withheld on such grounds, or any other grounds, please provide a written response with the following information:

(i) A description of the DOCUMENT or THING with sufficient particularity to IDENTIFY it for purposes of a court order, including without limitation

control numbers or Bates label numbers;

(ii) The DATE stated on the DOCUMENT or THINGS, or alternatively, the DATE it was created or first came into existence;

(iii) The nature of the protection claimed;

(iv) A list of all PERSONS who participated in the preparation of the DOCUMENT or THING;

(v) A list of all PERSONS who have received or reviewed copies of the DOCUMENT or THING; and

(vi) A list of all PERSONS to whom the DOCUMENT or THING was circulated, or its contents (if applicable) communicated.

G. Pursuant to Federal Rule of Civil Procedure 34, responsive DOCUMENTS and THINGS shall be produced as kept by its custodian in the ordinary course of business or shall be produced in a manner organized and labeled to correspond with the categories in these requests.

H. Pursuant to Federal Rule of Civil Procedure 34, in responding to these requests, you must make a diligent search of your records and of other papers or materials in your possession or available to you or your representatives. If, after exercising due diligence, you are unable to determine the existence of any DOCUMENTS or THINGS falling within a request, you shall so state in written responses.

I. If a refusal to provide DOCUMENTS or THINGS responsive to any request is asserted on the grounds of burdensomeness, you should state in detail the reason(s) for your objection(s), including the number and nature of documents or records needed to be searched and/or produced, the location of the documents, the custodian of the documents, and the number of person hours and costs required to conduct the search.

J. If any request is unclear or ambiguous to you, you are requested to contact undersigned counsel as soon as possible so that the request can be clarified to avoid unnecessary delays in discovery.

REQUESTS FOR PRODUCTION

REQUEST NO. 125:

DOCUMENTS CONCERNING all studies, tests, trials, research, or experiments conducted that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE, including without limitation all DOCUMENTS sufficient to IDENTIFY all PERSONS who have knowledge of such studies, tests, trials, research, or experiments, what knowledge each PERSON has, and all DOCUMENTS that evidence or refute such studies, tests, trials, research, or experiments.

REQUEST NO. 126:

DOCUMENTS submitted to the FDA and/or to the PTO that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

REQUEST NO. 127:

DOCUMENTS CONCERNING any and all statistical analyses conducted by, or on behalf of, or at the request of, in the custody or possession of WYETH, that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

REQUEST NO. 128:

All DOCUMENTS CONCERNING marketing plans for DESVENLAFAXINE that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

REQUEST NO. 129:

All education plans and DOCUMENTS to be provided to physicians or patients that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

REQUEST NO. 130:

All publications, including without limitation, U.S. and foreign patents, textbooks, articles, conference proceedings, treatises, theses, tutorials, speeches, and presentations, that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

REQUEST NO. 131:

All DOCUMENTS CONCERNING marketing plans or strategy to transition the market for EFFEXOR XR to any Wyeth formulation comprising DESVENLAFAXINE.

Dated: February 27, 2007

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IMPAX LABORATORIES, INC.

EXHIBIT E

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT F

Medical News TODAY www.medicalnewstoday.com

Wyeth Receives Approvable Letter From FDA For Pristiq (Desvenlafaxine Succinate) For The Treatment Of Major Depressive Disorder

24 Jan 2007 Click to Print

Wyeth Pharmaceuticals, a division of Wyeth (NYSE: WYE), announced today that the Company has received an approvable letter from the U.S. Food and Drug Administration (FDA) for Pristiq(TM) (desvenlafaxine succinate), a serotonin-norepinephrine reuptake inhibitor (SNRI) studied as a treatment for adult patients with major depressive disorder (MDD). The letter was received January 22.

"The approvable letter is in line with Wyeth's expectations and we remain on track with our plans for Pristiq," says Joseph Mahady, President, Wyeth Pharmaceuticals -- North America and Global Businesses. "We are working toward resolution of all outstanding issues at our manufacturing site in Guayama, Puerto Rico and have already made significant progress in meeting previously established commitments."

According to the approvable letter, FDA approval of Pristiq is subject to several conditions, including the following:

-- A satisfactory FDA inspection of the Company's Guayama, Puerto Rico facility, which is where Pristiq will be manufactured

-- Several post-marketing commitments, including submission of long-term relapse prevention, low dose and pediatric studies

-- Additional clarity around the Company's product education plan for physicians and patients

-- Confirmation by the FDA of the acceptability of the proprietary name, Pristiq

As the Company has already communicated, launch timing for the MDD indication is predicated on three elements -- final FDA approval for Pristiq as a treatment for adult patients with MDD, the results of ongoing MDD studies at lower dosage levels, and the progress of FDA review of Wyeth's separate New Drug Application (NDA) for vasomotor symptoms (VMS) associated with menopause. Importantly, while the approvable letter requires some post-marketing commitments, the FDA does not require that any additional clinical studies be submitted prior to the approval of Pristiq.

"Given the importance of Pristiq, we are committed to ensuring the most complete profile and product information is available to physicians and patients at the time of this product's launch," Mahady says.

About Pristiq

Pristiq is an SNRI studied as a potential treatment for adult men and women with MDD. Wyeth submitted a NDA for MDD on December 22, 2005. The Company has also filed a NDA for VMS associated with menopause and expects an FDA action letter in the second quarter of 2007. If approved, Pristiq will be the first and only non-hormonal medicine for the treatment of VMS associated with menopause. Wyeth is a leader in both neuroscience and women's health care.

Wyeth discovered and developed the first SNRI approved by the FDA, which is currently the most widely used antidepressant in the world. Pristiq represents Wyeth's latest efforts and continued commitment to developing therapies to help improve the lives of patients suffering from mental health disorders.

According to a large depression trial funded by the National Institute of Mental Health, only 28 percent of patients with depression achieved remission with initial antidepressant treatment. This leaves a

large percentage of patients still suffering from depression. Clearly, additional medicines are needed for treating MDD.

About Antidepressants

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder and other psychiatric disorders. Anyone considering the use of any antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are on such therapy should be observed closely for clinical worsening, suicidality or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with their prescriber.

About Major Depressive Disorder

Major depressive disorder is a serious medical condition that is different from "feeling blue" and is not something that people just "get over." Criteria for major depressive disorder include five or more of the following symptoms that have been present for at least two weeks, and at least one of the symptoms must be either depressed mood or loss of interest or pleasure.

-- Depressed mood

-- Loss of interest or pleasure

-- Changes in appetite or weight

-- Changes in sleeping patterns

-- Psychomotor agitation or retardation

-- Fatigue or low energy

-- Feeling worthless or guilty for no reason

-- Difficulty thinking or concentrating

-- Thoughts of death or suicide

Further, people with major depressive disorder may experience clinically significant distress or impairment in social, occupational or other important areas of functioning. If a person experiences these symptoms, he or she should speak with a health care professional.

Major depressive disorder is a common mental disorder, affecting about 121 million people worldwide. In the United States, it is estimated that depression affects about 19 million American adults each year. The lifetime risk of major depression has been assessed from 10 to 25 percent for women and five to 12 percent for men. Research has shown that hormonal changes, including estrogen decline, or life stressors experienced by women may contribute to a major depressive episode.

About Wyeth Pharmaceuticals

Wyeth Pharmaceuticals, a division of Wyeth, has leading products in the areas of women's health care, cardiovascular disease, central nervous system, inflammation, hemophilia, oncology and vaccines. Wyeth is one of the world's largest research-driven pharmaceutical and health care products companies. It is a leader in the discovery, development, manufacturing, and marketing of pharmaceuticals, vaccines, biotechnology products and nonprescription medicines that improve the quality of life for people worldwide. The Company's major divisions include Wyeth Pharmaceuticals, Wyeth Consumer Healthcare and Fort Dodge Animal Health.

The statements in this press release that are not historical facts are forward-looking statements based on current expectations of future events and are subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. These risks and uncertainties include risks associated with the inherent uncertainty of the timing and success of product research, development and commercialization (including with respect to our pipeline

products), drug pricing and payment for our products by government and third party-payors, manufacturing, data generated on the safety and efficacy of our products, economic conditions including interest and currency exchange rate fluctuations, changes in generally accepted accounting principles, the impact of competitive or generic products, trade buying patterns, global business operations, product liability and other types of litigation, the impact of legislation and regulatory compliance, intellectual property rights, strategic relationships with third parties, environmental liabilities, and other risks and uncertainties, including those detailed from time to time in our periodic reports filed with the Securities and Exchange Commission, including our current reports on Form 8-K, quarterly reports on Form 10-Q and annual report on Form 10-K, particularly the discussion under the caption "Item 1A, Risk Factors." We assume no obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

For more information, visit http://www.wyeth.com.

Wyeth Pharmaceuticals
http://www.wyeth.com

Article URL: http://www.medicalnewstoday.com/medicalnews.php?newsid=61459

EXHIBIT G

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	C. A. No. 06-222 (JJF)

PLAINTIFF'S RESPONSES AND OBJECTIONS TO IMPAX'S FOURTH REQUEST FOR PRODUCTION OF DOCUMENTS AND THINGS (NOS.125-131)

Plaintiff, Wyeth, hereby responds to Impax's Fourth Request for Production of Documents and Things (Nos. 125-131) served by Defendant Impax Laboratories, Inc. (hereinafter "Impax") on February 27, 2007.

GENERAL OBJECTIONS

1. Wyeth objects to any request to the extent it seeks to impose on Wyeth any obligation not required by the Federal Rules of Civil Procedure or the local rules of the United States District Court for the District of Delaware.

2. Wyeth objects generally to the production of documents and things protected by the attorney-client privilege, work product immunity, or any other applicable privilege. To the extent that such documents and things not otherwise objectionable are called for by Impax's requests, they will be identified in a listing of withheld documents

which will be prepared in due course and exchanged with Impax on a mutually agreed upon date.

3. An objection based on attorney-client privilege and/or work product immunity should not be construed as a representation that such documents exist or existed. Such objections indicate only that the requests are of such a scope as to embrace subject matter protected by the attorney-client privilege and/or work product immunity.

4. Wyeth objects generally to Impax's document requests to the extent they seek production of documents and things containing both discoverable and nondiscoverable or objectionable material. Wyeth reserves the right to redact any matter which is not called for or with respect to which Wyeth has objected to the request for production.

5. Wyeth objects to Impax's instructions to the extent they include within the definition of Wyeth's possession, custody or control all documents to which Wyeth has any access, however remote. Thus, Wyeth objects to Impax's document requests to the extent they seek to require Wyeth to provide any information beyond what is available to Wyeth at present from a reasonable search of its own files at its principal offices and pharmaceutical product research and development facilities in the United States and from reasonable inquiry of its present employees on the grounds that such discovery is irrelevant, unreasonably cumulative and unduly burdensome. Subject to these objections, Wyeth will use reasonable diligence to locate responsive documents in its possession, custody, and control based on an examination of those files reasonably expected to yield responsive documents.

6. As used in these responses, the phrase "all documents," or similar phrases, should be understood to mean those documents Wyeth and its counsel were able to locate using reasonable diligence and judgment concerning the existence and whereabouts of responsive documents. Such phraseology should not be construed as a representation that each and every document available to Wyeth has been examined in connection with these responses or any production pursuant thereto.

7. Wyeth's objections and responses are based on the best knowledge and information known to them at this time. Wyeth's objections and responses are made without prejudice to Wyeth's right to revise or supplement them based on the discovery taken in this case. Further, Wyeth's objections and responses are based on Wyeth's good-faith interpretation of the individual requests for production and are subject to correction for errors or omission, if any.

8. Wyeth objects to the production of documents in the public domain because the burden of obtaining access to, copying, and production is equal for both parties. Subject to this General Objection, and to the extent not otherwise objectionable, Wyeth will not seek to exclude from production, responsive public documents within its possession, custody, and control.

9. A response that documents will be produced should not be construed as a representation that such documents exist or existed. Such responses indicate only that documents responsive to the request, subject to applicable objections, will be produced if any such documents are found after a reasonable search.

10. To the extent that Impax's document requests seek the production of internal work product files from any of Wyeth's counsel, including, but not limited to,

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P. and Morris, Nichols, Arsht & Tunnell, L.L.P., Wyeth objects to either the production or the listing of these documents on a withheld document list.

11. Wyeth objects to the production of documents and things subject to the rights of third parties not affiliated with Wyeth. In addition, Wyeth objects to the production of non-Wyeth documents or information subject to a protective order entered in a litigation other than the above-captioned litigation.

12. Wyeth objects to Impax's definition of the terms "WYETH" or "PLAINTIFF." This action involves Wyeth and not its past or present, U.S. or foreign subsidiaries, past or present, U.S. or foreign divisions, or "any related companies." In addition, Wyeth objects to Impax's definition of "WYETH" or "PLAINTIFF" to the extent these terms include former officers, directors, employees, agents, attorneys or representatives as potentially including entities outside of Wyeth's possession, custody, or control, and as calling for information that may be subject to confidentiality agreements and/or attorney-client privilege. Consequently, in answering Impax's requests, Wyeth will construe "WYETH" and "PLAINTIFF" to mean only those portions of Wyeth involved with the research and development, manufacture, distribution, and/or sale of the venlafaxine hydrochloride extended release product EFFEXOR® XR in the United States. Wyeth further objects to Impax's instructions as unduly burdensome to the extent they seek to impose any further limitations or obligations upon Wyeth with respect to the production of documents within Wyeth's possession, custody, or control other than those set forth above.

13. Wyeth objects to the production of "electronically produced, electronically stored, photostatic, photographed, recorded, or otherwise reproduced communications or records of every kind and description," documents as well as "computer files, including backup or archival copies" as overly broad, unreasonably cumulative and unduly burdensome. Wyeth also objects to the term "CONCERNING" as vague, ambiguous, overly broad and unduly burdensome.

14. Wyeth objects to Impax's requests to the extent they call for information (including listing on a withheld document log) or documents generated subsequent to the February 10, 2003 cut-off date observed in the Teva litigation as irrelevant, overly broad, unduly burdensome and not reasonably calculated to lead to the discovery of admissible evidence. The production or listing on a withheld document log of any document or information generated subsequent to this date should not be construed as a waiver of this objection with respect to any other document or information.

15. Wyeth objects to the production of documents relating to ongoing clinical trials that are not complete and/or not decoded, analyzed, or reported. Wyeth further objects to the production of information such as voluminous raw data and data compilations from *in vitro* testing, pre-clinical studies, or clinical trials as unduly burdensome, unreasonably cumulative, unreasonably duplicative and irrelevant.

16. Wyeth objects to the production of commercial, financial, regulatory, marketing, patent prosecution and proceedings, legal and other documents to the extent they concern countries other than the United States as unduly burdensome, overly broad, and/or irrelevant to any issue in the suit, and not reasonably calculated to lead to the discovery of admissible evidence.

17. Wyeth objects to the production of routine manufacturing, production, qualification, quality control, quality assurance, batch records, release records, and other routine testing as overly broad, irrelevant, unduly burdensome, unreasonably cumulative and duplicative, and not reasonably calculated to lead to the discovery of admissible evidence.

18. The incidental production of any document or information covered by any of Wyeth's General or Specific Objections shall not be construed as a waiver of the objection with respect to any other document or information.

19. Nothing in these responses should be construed as waiving rights or objections which otherwise might be available to Wyeth, nor should Wyeth's answering any discovery request be deemed an admission of relevancy, materiality or admissibility in evidence of the discovery requests or the responses thereto.

20. The General Objections apply to all of Impax's Document Request Nos. 125-131. To the extent that specific General Objections are cited herein in response to specific document requests, those specific citations are provided because they are believed to be particularly applicable to the request and are not to be construed as a waiver of any other General Objections applicable to documents falling within the scope of the request.

21. Wyeth maintains the General and Specific Objections it made in response to requests for production propounded by Defendants in the Teva litigation and hereby incorporates by reference herein all of those General and Specific Objections and Responses.

22. Although Wyeth objects generally to Impax's request that documents and things be produced at the offices of Heller Ehrman, LLP, Wyeth will forward to the offices of Heller Ehrman, LLP copies of produced documents. Nevertheless, Wyeth retains the right to produce documents or things by making them available for inspection and copying by Impax at Wyeth's or Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.'s facilities.

23. Wyeth objects to Impax's Definitions and Instructions to the extent they seek to impose on Wyeth obligations not required by the Federal Rules of Civil Procedure or the local rules of the United States District Court for the District of Delaware and as overly burdensome.

24. Wyeth objects to Impax's definition of "NAMED INVENTOR" to the extent it encompasses persons beyond Deborah M. Sherman, John C. Clark, John U. Lamer and Stephen A. White as vague and ambiguous, overly broad, unduly burdensome, and irrelevant to any issue in the suit.

24. Wyeth objects to Impax's definition of "ALZA" as vague, ambiguous, encompassing entities outside of Wyeth's possession, custody, or control, and as potentially calling for information that may be subject to confidentiality agreements and/or attorney-client privilege.

24. Wyeth objects to Impax's definition of "DESVENLAFAXINE" as vague, ambiguous, overly broad, and unduly burdensome, and not reasonably calculated to lead to the discovery of admissible evidence, to the extent it encompasses "compositions, formulations, and preparations containing venlafaxine."

RESPONSES

IMPAX DOCUMENT REQUEST NO. 125:

DOCUMENTS CONCERNING all studies, tests, trials, research, or experiments conducted that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE, including without limitation all DOCUMENTS sufficient to IDENTIFY all PERSONS who have knowledge of such studies, tests, trials, research, or experiments, what knowledge each PERSON has, and all DOCUMENTS that evidence or refute such studies, tests, trials, research, or experiments.

OBJECTION:

The present suit concerns Impax's attempts to seek approval to market Venlafaxine HCl Extended-Release Capsules and has no bearing on comparisons between extended release formulations of venlafaxine and any formulation comprising desvenlafaxine. Impax has not provided any nexus between the need for such documents and their relevance to any claim or defense. Wyeth therefore objects to this request to the extent it seeks documents that "compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE" as not reasonably calculated to lead to the discovery of admissible evidence and irrelevant to any issue in this suit.

Wyeth further objects to this document request to the extent it seeks information concerning (1) any formulation comprising desvenlafaxine, and/or (2) any venlafaxine-containing extended release formulation developed after the effective filing date of the patents-in-suit, other than EFFEXOR® XR, as overly broad, unduly burdensome, irrelevant to any issue in the suit, not reasonably calculated to lead to the discovery of admissible evidence and as seeking highly sensitive future product information.

Wyeth objects to this request as overly broad, unduly burdensome, vague and ambiguous, and not reasonably calculated to lead to the discovery of admissible evidence to the extent it calls for documents "CONCERNING all studies, tests, trials, research, or experiments conducted." Wyeth further objects to this request as overly broad and unduly burdensome to the extent it seeks the production of information such as voluminous raw data and data compilations from clinical trials, manufacturing, production, quality control, quality assurance, and documents containing patient identifying information that would raise privacy issues.

Wyeth further objects to this request as overly broad, unduly burdensome, vague and ambiguous, and not reasonably calculated to lead to the discovery of admissible evidence to the extent it calls for documents "sufficient to IDENTIFY all PERSONS who have knowledge" of such activities, insofar as this request potentially encompasses hundreds of Wyeth employees involved in all aspects of clinical trials, routine testing, scale-up, maintenance, purchasing or qualification of raw materials and equipment, manufacturing, packaging, quality control, quality assurance etc. who would have, at best, a tangential association to any comparison of "nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE." Wyeth also objects to this request to the extent it seeks "all studies, tests, trials, research, or experiments" as vague and ambiguous, overly broad and unduly burdensome. Wyeth further objects to this request as overly broad, unduly burdensome, vague, ambiguous, and not reasonably calculated to lead to the discovery

of admissible evidence to the extent it calls for documents that "evidence or refute" such studies, tests, trials, research, or experiments.

Wyeth further objects to this request to the extent it seeks the production of sensitive patient information as unduly burdensome, cumulative, duplicative and irrelevant. The burden of collecting, reviewing, and redacting sensitive patient identifying information outweighs any possible, marginal relevance such information would have. Wyeth also objects to this request to the extent it seeks the production of documents relating to ongoing clinical trials that are not complete and/or not decoded, analyzed, or reported.

Wyeth further objects to this request to the extent that it seeks documents that are protected by the attorney-client privilege, prepared, or obtained in anticipation of litigation or for trial, or are otherwise subject to the work product doctrine or any other applicable rights, privilege, or immunity.

IMPAX DOCUMENT REQUEST NO. 126:

DOCUMENTS submitted to the FDA and/or to the PTO that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

OBJECTION:

The present suit concerns Impax's attempts to seek approval to market Venlafaxine HCl Extended-Release Capsules and has no bearing on comparisons between extended release formulations of venlafaxine and any formulation comprising desvenlafaxine. Impax has not provided any nexus between the need for such documents and their relevance to any claim or defense. Wyeth therefore objects to this

request to the extent it seeks documents that "compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE" as not reasonably calculated to lead to the discovery of admissible evidence and irrelevant to any issue in this suit.

Wyeth further objects to this request to the extent it seeks information concerning (1) any formulation comprising desvenlafaxine, and/or (2) any venlafaxine-containing extended release formulation developed after the effective filing date of the patents-in-suit, other than EFFEXOR® XR, as overly broad, unduly burdensome, irrelevant to any issue in the suit, not reasonably calculated to lead to the discovery of admissible evidence, and as seeking highly sensitive future product information. Likewise, Wyeth objects to this request to the extent it seeks the production of documents relating to any attempt to seek patent protection or FDA approval for any formulation or method involving desvenlafaxine as overly broad, unduly burdensome, irrelevant to any issue in this suit, and not reasonably calculated to lead to the discovery of admissible evidence.

Wyeth further objects to this request to the extent that it seeks documents that are protected by the attorney-client privilege, prepared, or obtained in anticipation of litigation or for trial, or are otherwise subject to the work product doctrine or any other applicable rights, privilege, or immunity.

IMPAX DOCUMENT REQUEST NO. 127:

DOCUMENTS CONCERNING any and all statistical analyses conducted by, or on behalf of, or at the request of, in the custody or possession of WYETH, that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

OBJECTION:

Wyeth herein incorporates its General and Specific Objections to Impax Document Request Nos. 125. Wyeth further objects to the term "statistical analyses" that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE as vague, ambiguous, overly broad, not reasonably calculated to lead to the discovery of admissible evidence, and irrelevant to any issue in this litigation.

IMPAX DOCUMENT REQUEST NO. 128:

All DOCUMENTS CONCERNING marketing plans for DESVENLAFAXINE that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

OBJECTION:

Wyeth herein incorporates its General and Specific Objections to Impax Document Request No. 125. Wyeth further objects to Impax's request for "marketing plans" relating to desvenlafaxine as vague, ambiguous, overly broad, not reasonably calculated to lead to the discovery of admissible evidence, and irrelevant to any issue in this litigation. Wyeth further objects to the production of marketing information relating to desvenlafaxine as seeking highly sensitive commercial information regarding a future product not at issue in this litigation.

IMPAX DOCUMENT REQUEST NO. 129:

All education plans and DOCUMENTS to be provided to physicians or patients that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

OBJECTION:

Wyeth herein incorporates its General and Specific Objections to Impax Document Request Nos. 125. Wyeth further objects to Impax's request for "education plans and DOCUMENTS to be provided to physicians or patients" relating to desvenlafaxine as vague, ambiguous, overly broad, not reasonably calculated to lead to the discovery of admissible evidence, and irrelevant to any issue in this litigation. Wyeth further objects to the production of any educational, informational, or promotional materials relating to desvenlafaxine as seeking highly sensitive information regarding a future product not at issue in this litigation.

IMPAX DOCUMENT REQUEST NO. 130:

All publications, including without limitation, U.S. and foreign patents, textbooks, articles, conference proceedings, treatises, theses, tutorials, speeches, and presentations, that compare nausea and emesis between patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE and patients receiving DESVENLAFAXINE.

OBJECTION:

Wyeth herein incorporates its General and Specific Objections to Impax Document Request No. 125. Wyeth further objects to this request to the extent it seeks documents from "U.S. and foreign patents, textbooks, articles, conference proceedings, treatises, theses, tutorials, speeches, and presentations" as encompassing documents outside of Wyeth's possession, custody and control and/or subject to the rights of third

parties. Wyeth further objects to the production of any non-public materials relating to desvenlafaxine as seeking highly sensitive information regarding a future product not at issue in this litigation. To the extent Impax's request would require Wyeth to search through publicly available literature or seeks documents available to Impax from the public domain, this request is overly broad, unduly burdensome and unreasonable. Such printed publications are already available to Impax and Impax can search for such documents on its own.

IMPAX DOCUMENT REQUEST NO. 131:

All DOCUMENTS CONCERNING marketing plans or strategy to transition the market for EFFEXOR XR to any WYETH formulation comprising DESVENLAFAXINE.

OBJECTION:

Wyeth herein incorporates its General and Specific Objections to Impax Document Request Nos. 125 and 128. Wyeth further objects to Impax's request for "marketing plans or strategy to transition the market" relating to desvenlafaxine as vague, ambiguous, overly broad, not reasonably calculated to lead to the discovery of admissible evidence, and irrelevant to any issue in this litigation. Wyeth further objects to the production of "marketing plans or strategy" relating to desvenlafaxine as seeking highly sensitive commercial information regarding a future product not at issue in this litigation.

Dated: March 29, 2007

By:

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Attorneys for Plaintiff Wyeth

CERTIFICATE OF SERVICE

I, Robert A. Pollock, hereby certify that on the 29th day of March 2007, I caused a true and correct copy of PLAINTIFF'S RESPONSES AND OBJECTIONS TO IMPAX'S FOURTH REQUEST FOR PRODUCTION OF DOCUMENTS AND THINGS (NOS.125-131), to be served by Federal Express, priority overnight delivery, upon the following:

Attorneys for IMPAX LABORATORIES, INC.

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San Francisco, CA 94104

Mary B. Matterer, Esq.
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Robert A. Pollock

EXHIBIT H

HellerEhrman LLP

April 4, 2007

Via E-mail and U.S. Mail

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Re: *Wyeth v. Impax Laboratories, Inc.*
U.S. District Court, District of Delaware, Civil Action No. 06-222 JJF

Dear Mr. Pollock:

This summarizes our meet and confer yesterday and responds to the portion of your letter dated April 3, 2007 regarding that telephone conference. Unfortunately, in the call we were unable to reach agreement as to the relevance of the desvenlafaxine documents requested in Impax's Fourth Set of Requests for Production of Documents and Things (Nos. 125-131) or those requested in Requests Nos. 7 and 8 accompanying the Notice of Subpoena to Lynn A. Cunningham, M.D. Ultimately, Ms. Rudolph stated that neither Wyeth nor Dr. Cunningham would produce any documents responsive to these requests. Moreover, neither Wyeth nor Dr. Cunningham would identify the quantity or whereabouts of documents in these categories, nor would Ms. Rudolph respond to our inquiry as to whether Dr. Cunningham even has any such documents in his possession.

Impax's Fourth Set of Requests for Production of Documents and Things to Wyeth seeks documents from Wyeth that generally relate to studies and research comparing nausea and emesis between patients who receive a Wyeth extended release venlafaxine formulation and patients who receive the related desvenlafaxine, a known and admitted metabolite of desvenlafaxine. They also request marketing documents that compare nausea and emesis between patients who receive a Wyeth extended release venlafaxine formulation and patients who receive desvenlafaxine, as well as marketing plans or strategy to transition the market from Effexor XR to desvenlafaxine.

Requests for Documents and Things Nos. 7 and 8 accompanying the Notice of Subpoena to Lynn A. Cunningham, M.D. seek documents from Dr. Cunningham that compare nausea and emesis between patients who receive a Wyeth extended release

venlafaxine formulation and patients who receive desvenlafaxine, as well as documents concerning nausea and emesis associated with the administration of desvenlafaxine.

As I explained in the meet and confer yesterday, we believe this information is relevant to several issues in this case, including inequitable conduct and commercial success, and is, at the very least, likely to lead to admissible evidence on those issues. Some of the asserted claims of the patents-in-suit require "diminished incidence of nausea and emesis," and Wyeth made representations to the Patent Office regarding this alleged "diminished incidence." Wyeth has placed this issue in controversy and must now produce all documents that could prove or disprove or frame the issues relating to it. Studies that compare nausea and emesis between patients who receive a Wyeth extended release venlafaxine formulation and patients who receive desvenlafaxine would necessarily include nausea and emesis data that may contradict Wyeth's representations regarding the alleged "diminished incidence." The assertion in your letter of yesterday that such documents have no relevance on the issue of inequitable conduct because Wyeth did not make direct statements to the Patent Office about comparisons of venlafaxine and desvenlafaxine misses the point. Statements to the Patent Office do not define limits to discovery. Those are governed by the Federal Rules of Civil Procedure, which require liberal discovery of anything which might lead to any admissible evidence.

Documents concerning marketing plans or strategy to transition the market for Effexor XR to a Wyeth desvenlafaxine product are relevant to, *inter alia*, the alleged commercial success of Effexor XR because Wyeth intends to shift the market from Effexor XR to desvenlafaxine – its next generation product to follow Effexor XR. As such, any improvement in the reduction of nausea or emesis in patients who are administered desvenlafaxine bears on the commercial success of Effexor XR. Marketing plans and strategy documents on this subject are relevant to the lack of nexus between the patented invention and any alleged commercial success because they would discuss marketable features of both Effexor XR and the desvenlafaxine product and relative drawbacks of each for promotional purposes, including claimed features of the extended release venlafaxine. Again, Wyeth has framed the issues by its reliance on alleged "commercial success" to bolster its claims of patent validity. Therefore, we maintain that Wyeth's and Dr. Cunningham's refusals to produce any document in response to these requests are improper.

We believe we have clearly explained how the requested documents are relevant to issues in this case, or would at least lead to admissible evidence. As Ms. Rudolph stated during today's teleconference, we will have to "agree to disagree" as to the relevance of these documents at this time. Because Wyeth and Dr. Cunningham continue to object to Impax's document requests regarding desvenlafaxine and refuse to even conduct a reasonable search for such documents, let alone produce such documents, we are forced to seek assistance from the Court.

Sincerely,

Eric L. Lane

SD 873307 v1

EXHIBIT I

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT J

US006673838B2

(12) **United States Patent**
Hadfield et al.

(10) **Patent No.: US 6,673,838 B2**
(45) **Date of Patent: Jan. 6, 2004**

(54) **SUCCINATE SALT OF O-DESMETHYL-VENLAFAXINE**

(75) Inventors: **Anthony F. Hadfield**, Nanuet, NY (US); **Syed M. Shah**, East Hanover, NJ (US); **Michael W. Winkley**, Campbell Hall, NY (US); **Karen W. Sutherland**, New City, NY (US); **James A. Provost**, Waltham Chase (GB); **Aeri Park**, West Lafayette, IN (US); **Rex A. Shipplett**, Wolcott, IN (US); **Brenton W. Russell**, West Lafayette, IN (US); **Beat T. Weber**, Zofingen (CH)

(73) Assignee: **Wyeth**, Madison, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/073,743**

(22) Filed: **Feb. 11, 2002**

(65) **Prior Publication Data**

US 2003/0045583 A1 Mar. 6, 2003

Related U.S. Application Data

(60) Provisional application No. 60/268,214, filed on Feb. 12, 2001, and provisional application No. 60/297,963, filed on Jun. 13, 2001.

(51) **Int. Cl.**[7] **A61K 31/205**; C07C 55/00; C07C 211/00

(52) **U.S. Cl.** **514/554**; 562/590; 564/336

(58) **Field of Search** 514/554; 562/590; 564/336

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,535,186 A 8/1985 Husbands et al.

FOREIGN PATENT DOCUMENTS

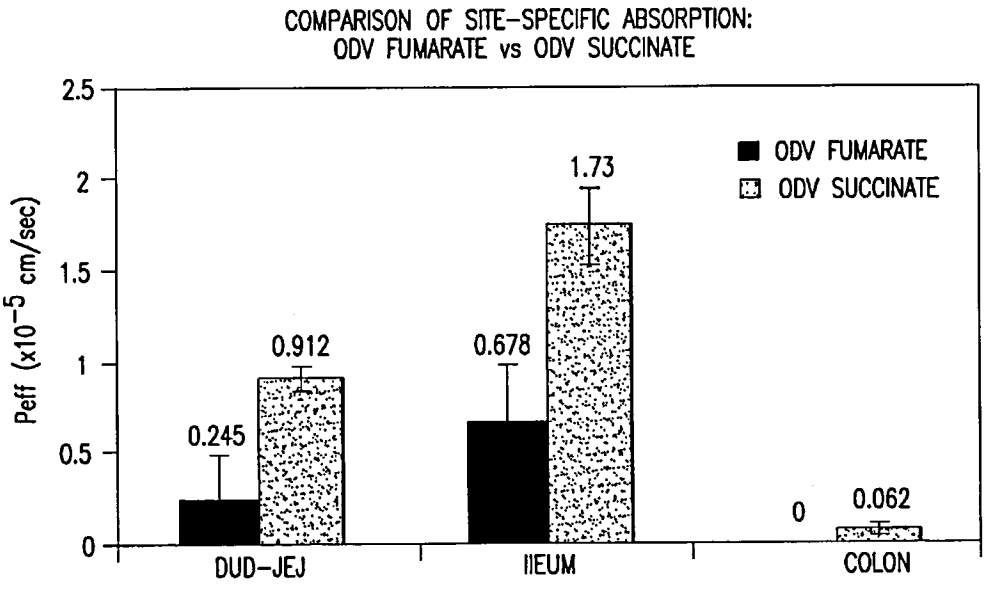
EP	0 112 669	7/1984
WO	WO 00/32555	6/2000
WO	WO 00/59851	10/2000
WO	WO 00/76955	12/2000

Primary Examiner—Samuel Barts
Assistant Examiner—Paul A. Zucker
(74) *Attorney, Agent, or Firm*—Rebecca R. Barrett

(57) **ABSTRACT**

A novel salt of O-desmethyl venlafaxine is provided, O-desmethylvenlafaxine succinate. Pharmaceutical compositions, dosage forms and methods of use are also provided.

46 Claims, 12 Drawing Sheets



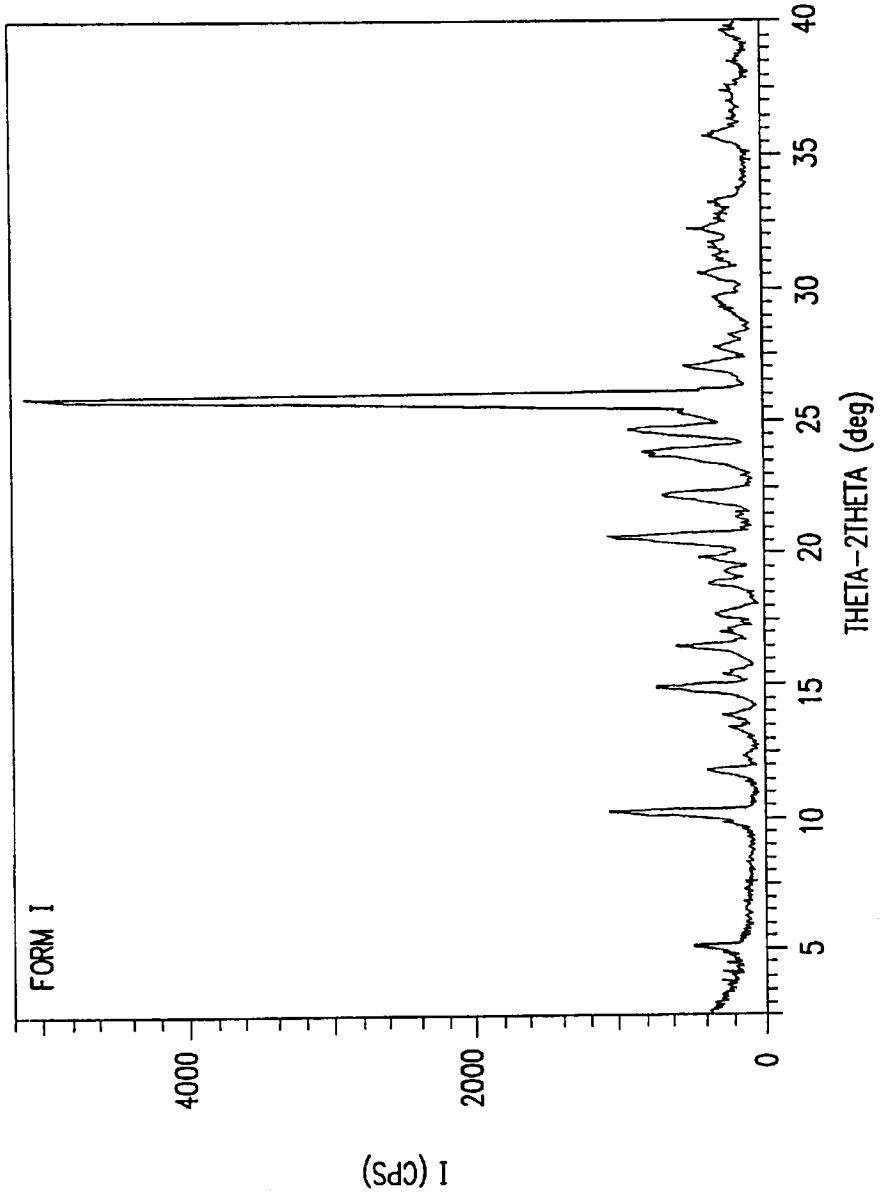


FIG. 1

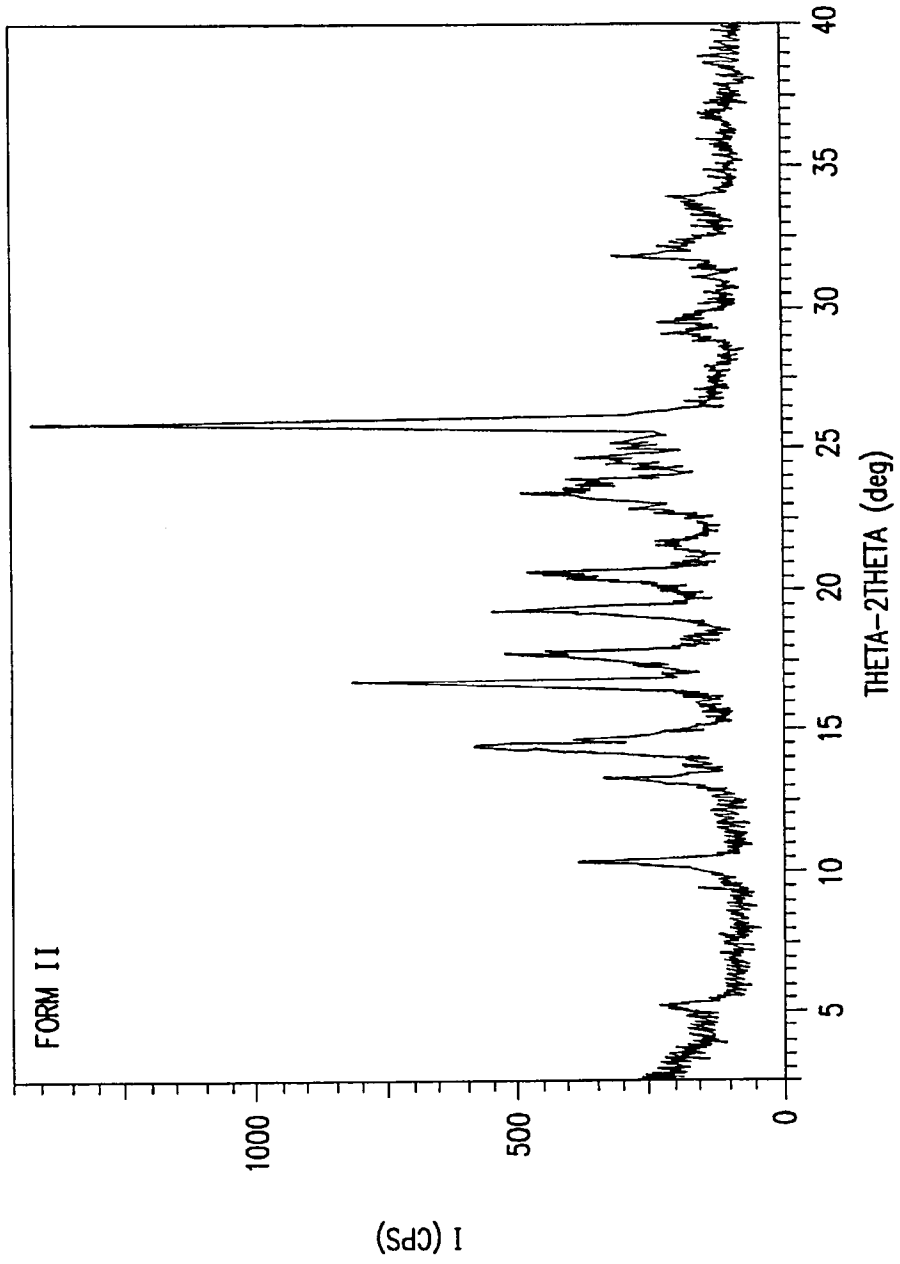


FIG.2

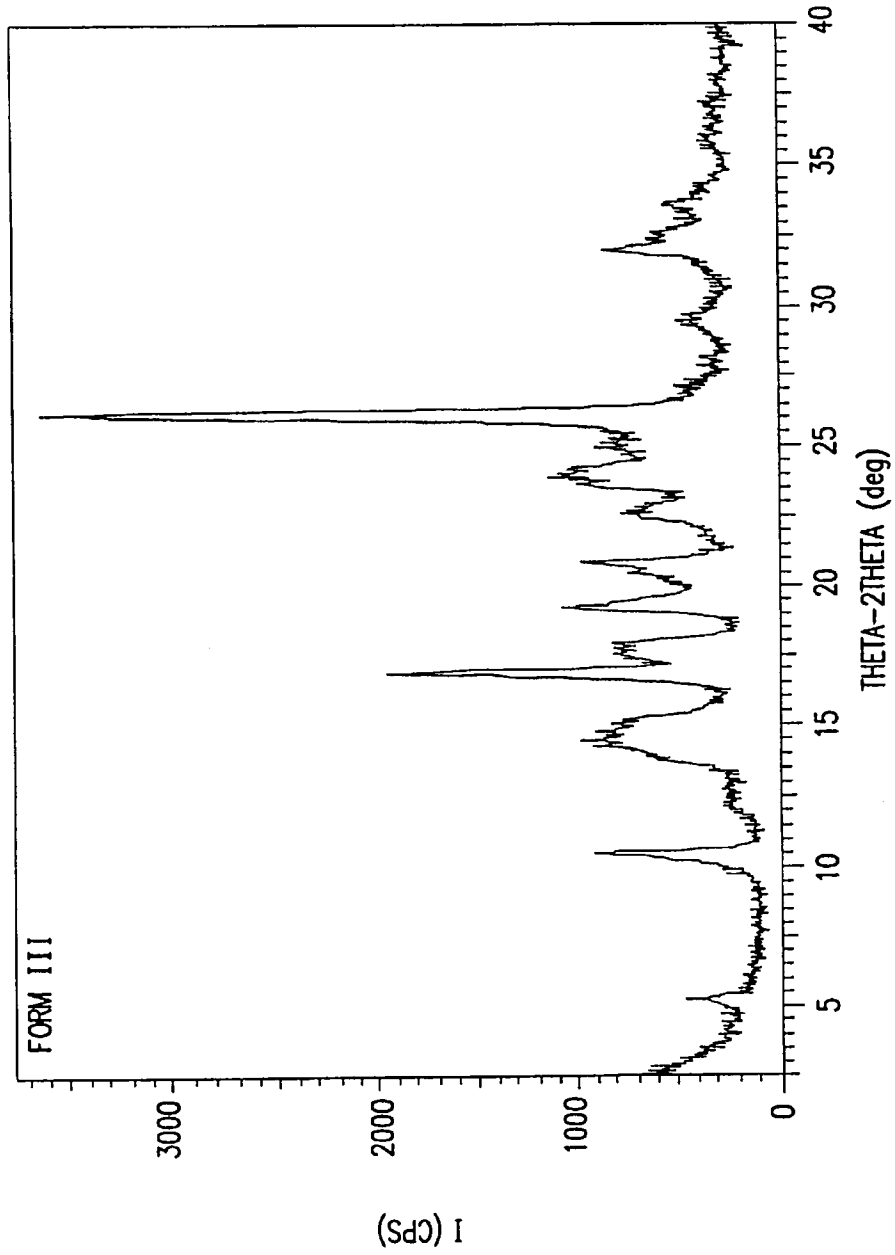

FORM III
I (CPS)
0
1000
2000
3000
5
10
15
20
25
30
35
40
THETA-2THETA (deg)

FIG.3

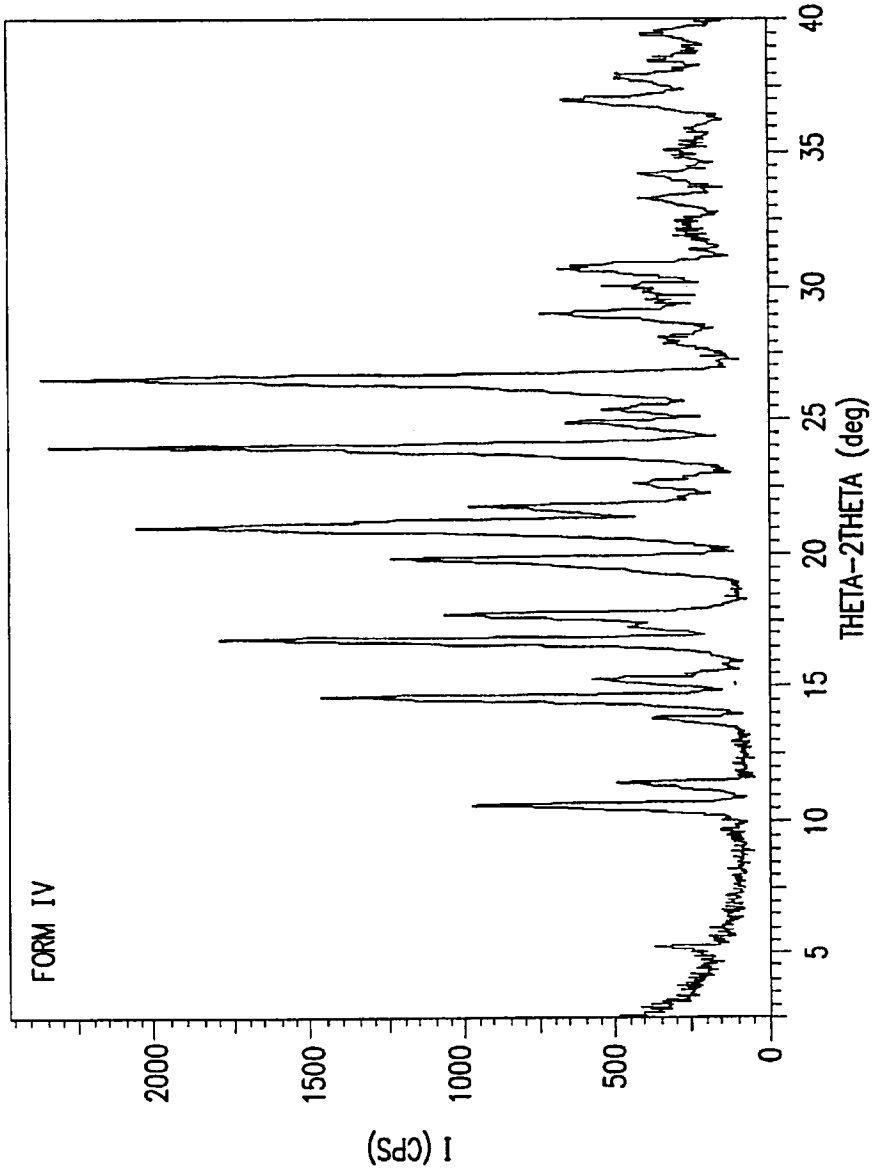

FORM IV
I (CPS)
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
THETA-2THETA (deg)

FIG.4

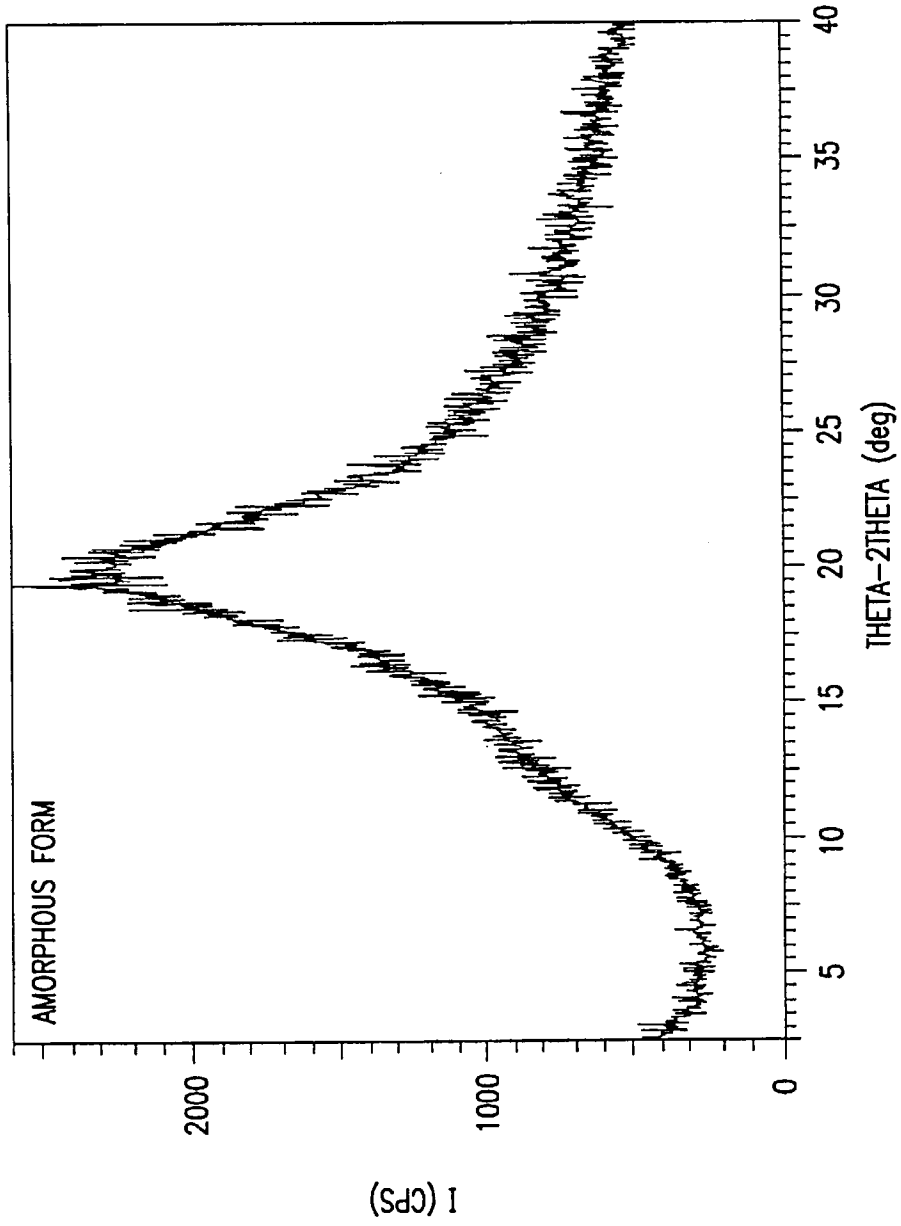

AMORPHOUS FORM
I (CPS)
2000
1000
0
5
10
15
20
25
30
35
40
THETA-2THETA (deg)

FIG.5

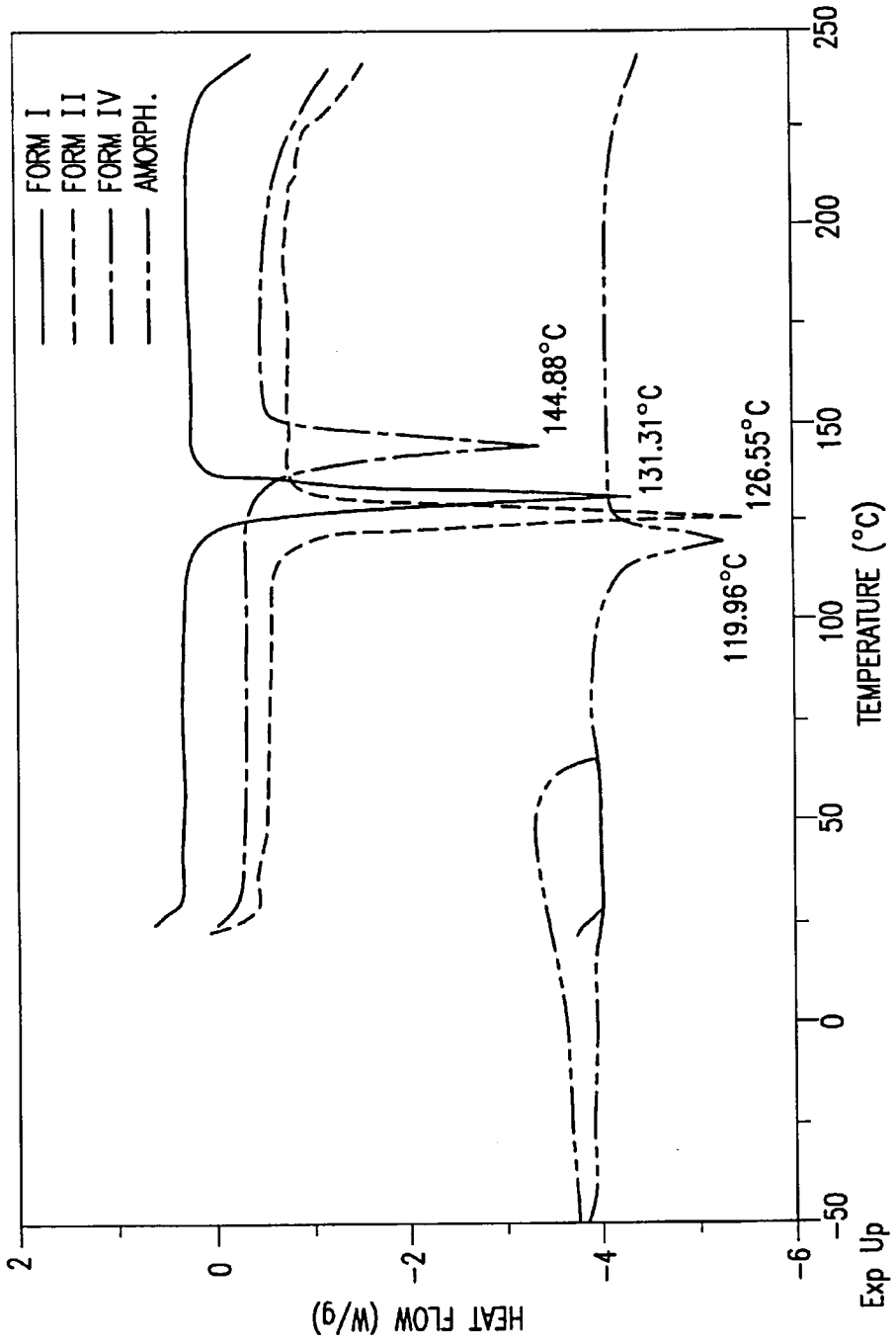

FORM I
FORM II
FORM IV
AMORPH.
144.88°C
131.31°C
126.55°C
119.96°C
HEAT FLOW (W/g)
TEMPERATURE (°C)
Exp Up
2
0
-2
-4
-6
250
200
150
100
50
0
-50

FIG.6

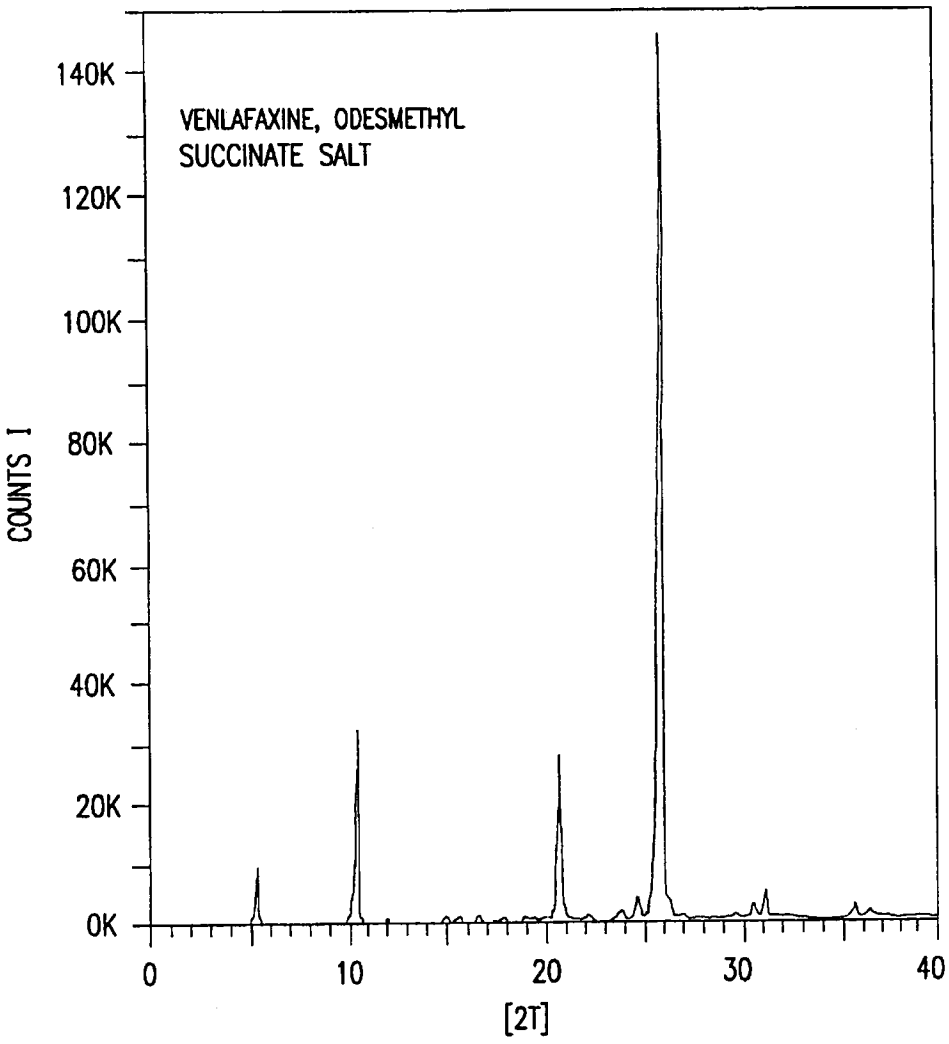

VENLAFAXINE, ODESMETHYL
SUCCINATE SALT
140K
120K
100K
80K
60K
40K
20K
0K
COUNTS I
0
10
20
30
40
[2T]

FIG.7

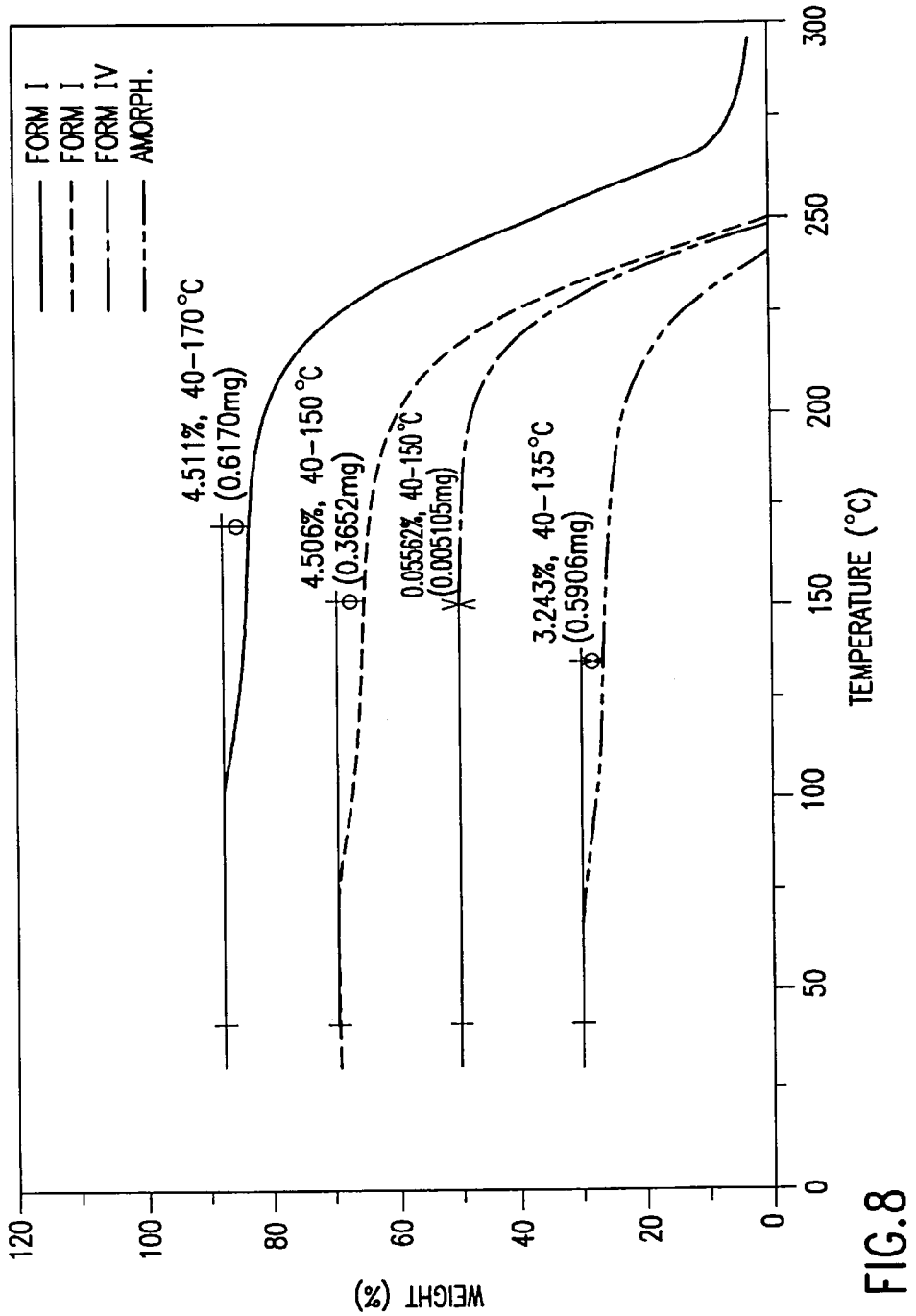

FORM I
FORM I
FORM IV
AMORPH.
4.511%, 40–170 °C
(0.6170mg)
4.506%, 40–150 °C
(0.3652mg)
0.05562%, 40–150 °C
(0.005105mg)
3.243%, 40–135 °C
(0.5906mg)
WEIGHT (%)
TEMPERATURE (°C)
0
20
40
60
80
100
120
0
50
100
150
200
250
300

FIG.8

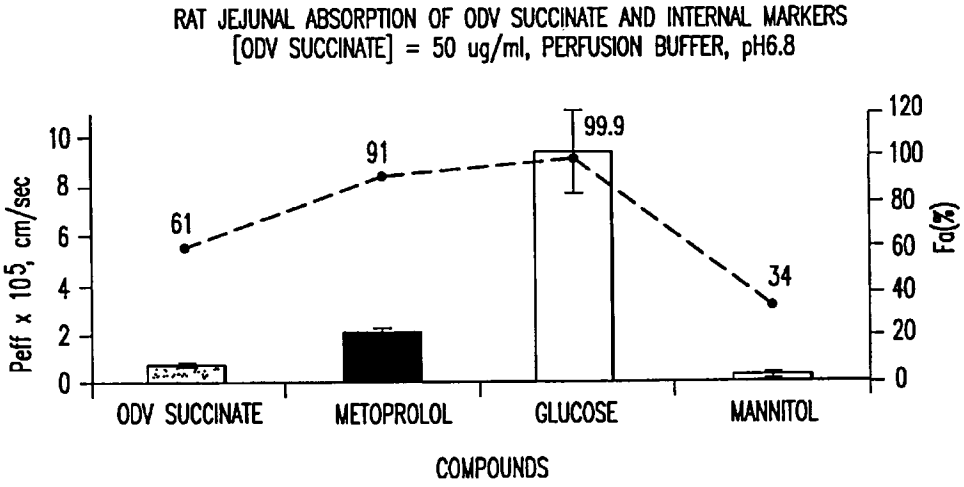

RAT JEJUNAL ABSORPTION OF ODV SUCCINATE AND INTERNAL MARKERS
[ODV SUCCINATE] = 50 ug/ml, PERFUSION BUFFER, pH6.8
Peff x 10^5, cm/sec
Fa(%)
61
91
99.9
34
ODV SUCCINATE
METOPROLOL
GLUCOSE
MANNITOL
COMPOUNDS

FIG.9

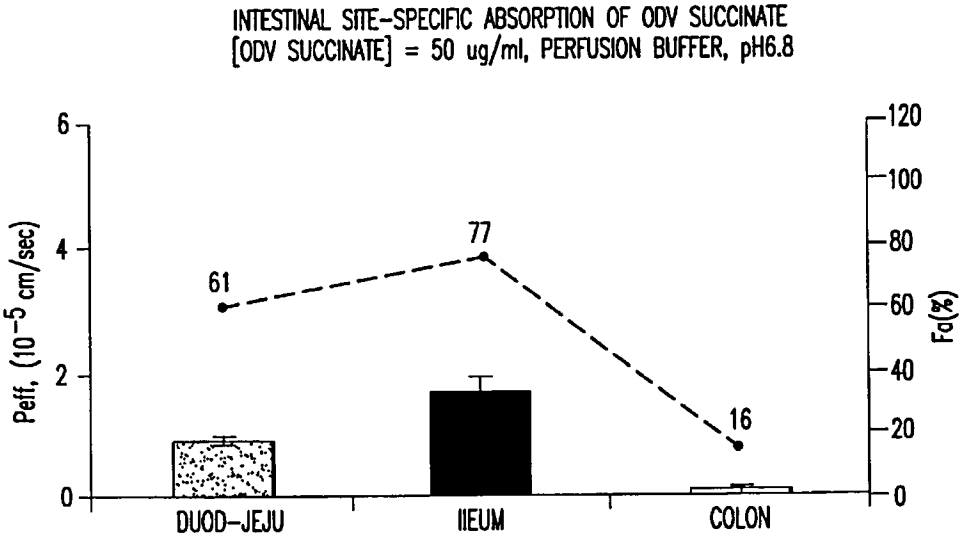

INTESTINAL SITE-SPECIFIC ABSORPTION OF ODV SUCCINATE
[ODV SUCCINATE] = 50 ug/ml, PERFUSION BUFFER, pH6.8
Peff, (10^-5 cm/sec)
Fa(%)
61
77
16
DUOD-JEJU
IIEUM
COLON

FIG.10

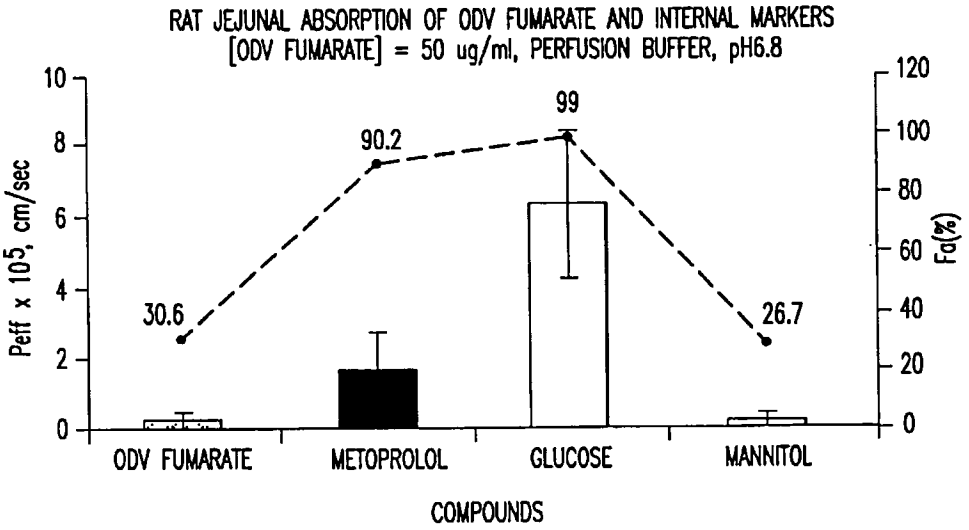

RAT JEJUNAL ABSORPTION OF ODV FUMARATE AND INTERNAL MARKERS
[ODV FUMARATE] = 50 ug/ml, PERFUSION BUFFER, pH6.8
Peff x 10^5, cm/sec
Fa(%)
30.6
90.2
99
26.7
ODV FUMARATE
METOPROLOL
GLUCOSE
MANNITOL
COMPOUNDS

FIG.11

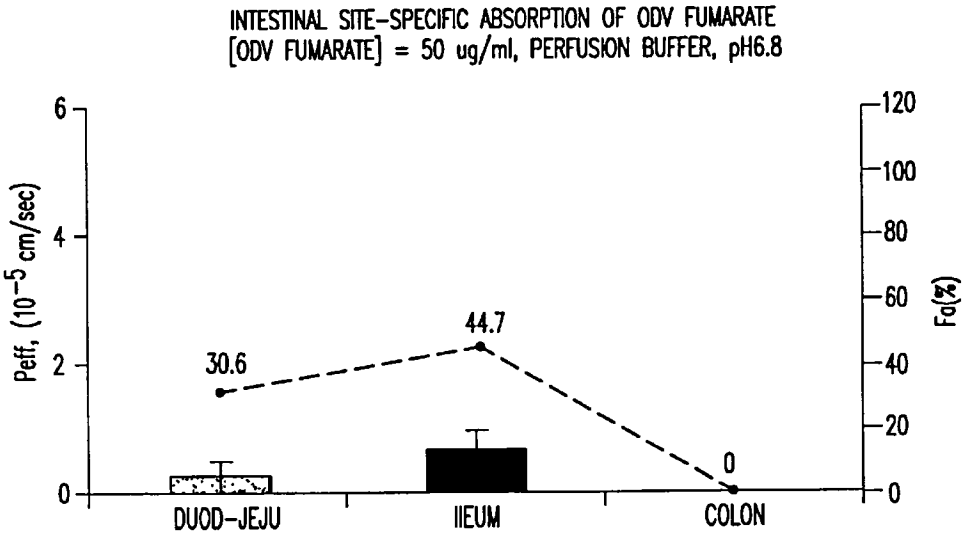

INTESTINAL SITE-SPECIFIC ABSORPTION OF ODV FUMARATE
[ODV FUMARATE] = 50 ug/ml, PERFUSION BUFFER, pH6.8
Peff, (10^-5 cm/sec)
Fa(%)
30.6
44.7
0
DUOD-JEJU
IIEUM
COLON

FIG.12

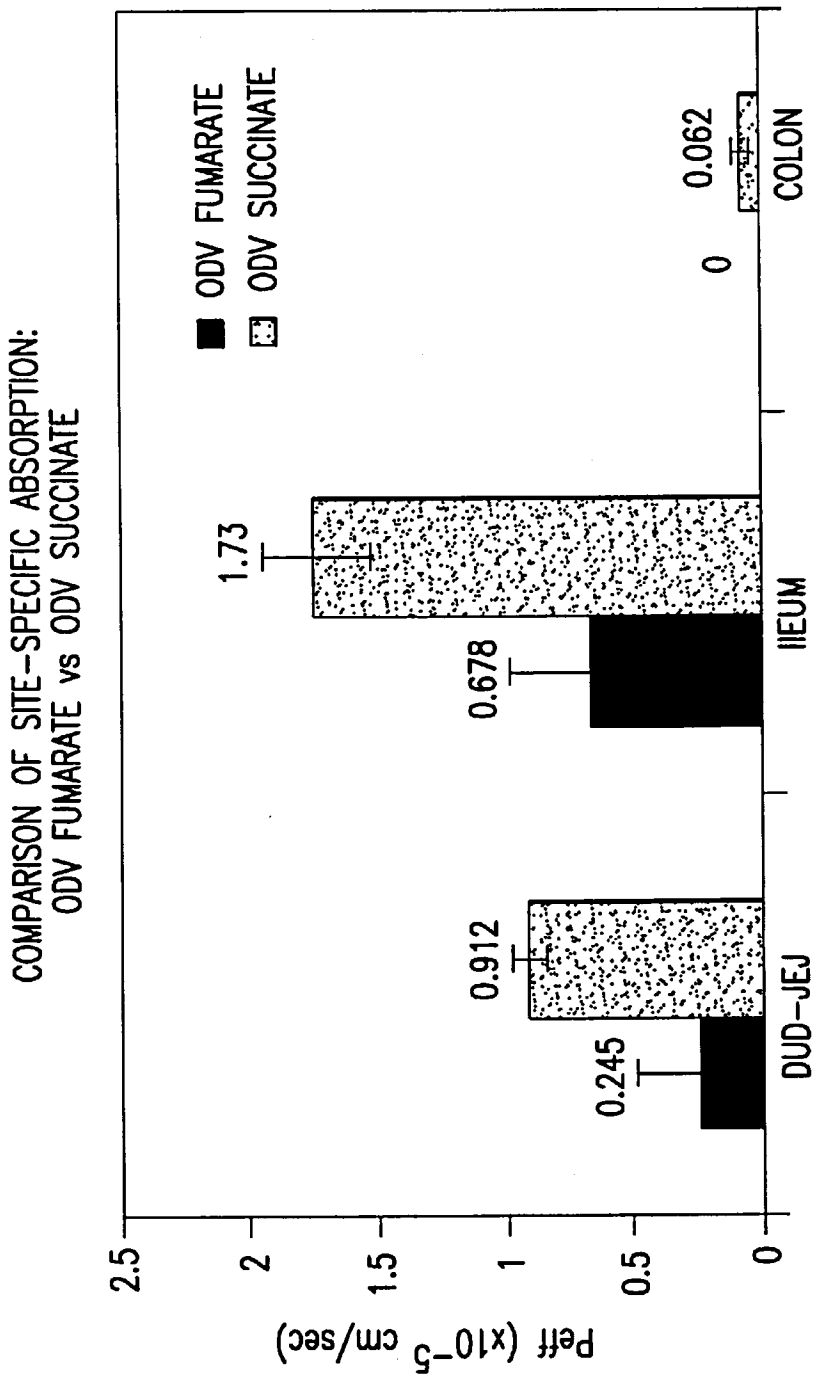

COMPARISON OF SITE-SPECIFIC ABSORPTION:
ODV FUMARATE vs ODV SUCCINATE
ODV FUMARATE
ODV SUCCINATE
Peff (x10⁻⁵ cm/sec)
2.5
2
1.5
1
0.5
0
1.73
0.678
0.912
0.245
0
0.062
DUD-JEJ
IIEUM
COLON

FIG. 13

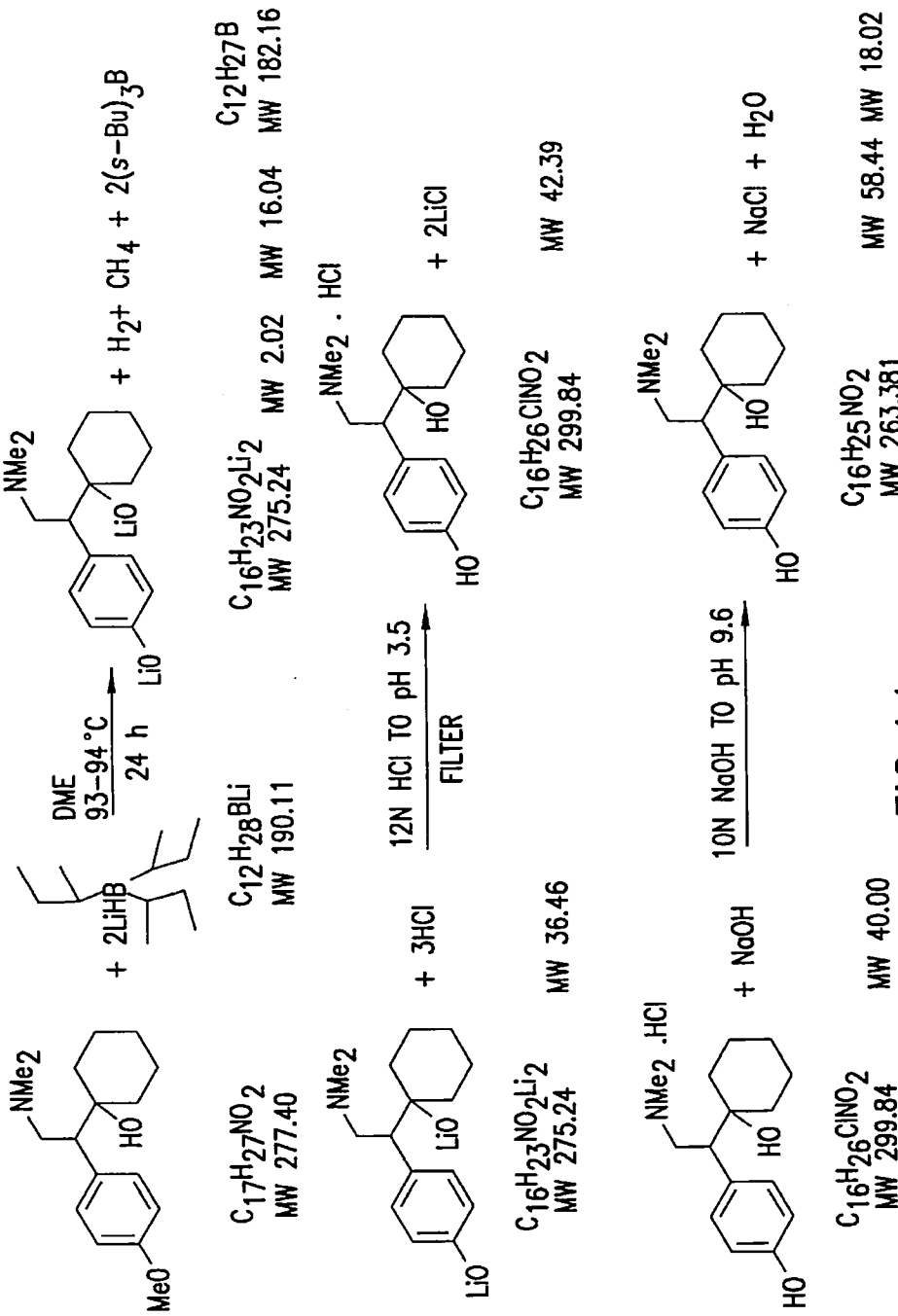

NMe2
HO
MeO
$C_{17}H_{27}NO_2$
MW 277.40
+ 2LiHB
$C_{12}H_{28}BLi$
MW 190.11
DME
93–94 °C
24 h
NMe2
LiO
LiO
$C_{16}H_{23}NO_2Li_2$
MW 275.24
+ H_2+ CH_4 + $2(s\text{-}Bu)_3B$
MW 2.02
MW 16.04
$C_{12}H_{27}B$
MW 182.16
NMe2
LiO
LiO
$C_{16}H_{23}NO_2Li_2$
MW 275.24
+ 3HCl
MW 36.46
12N HCl TO pH 3.5
FILTER
NMe2 . HCl
HO
HO
$C_{16}H_{26}ClNO_2$
MW 299.84
+ 2LiCl
MW 42.39
NMe2 .HCl
HO
HO
$C_{16}H_{26}ClNO_2$
MW 299.84
+ NaOH
MW 40.00
10N NaOH TO pH 9.6
NMe2
HO
HO
$C_{16}H_{25}NO_2$
MW 263.381
+ NaCl + H_2O
MW 58.44
MW 18.02

FIG. 14

SUCCINATE SALT OF O-DESMETHYL-VENLAFAXINE

This application claims priority from copending provisional application(s) serial No. 60/268,214 filed on Feb. 12, 2001 and 60/297,963 filed on Jun. 13, 2001.

FIELD OF THE INVENTION

The present invention provides a novel salt of O-desmethyl-venlafaxine, O-desmethyl-venlafaxine succinate, as well as polymorphs, pharmaceutical compositions, dosage forms, and methods of use with the same.

BACKGROUND OF THE INVENTION

O-desmethyl venlafaxine is a major metabolite of venlafaxine and has been shown to inhibit norepinephrine and serotonin uptake. Klamerus, K. J. et al., "Introduction of the Composite Parameter to the Pharmacokinetics of Venlafaxine and its Active O-Desmethyl Metabolite", *J. Clin. Pharmacol.* 32:716–724 (1992). O-desmethyl-venlafaxine, chemically named 1-[2-(dimethylamino)-1-(4-phenol) ethyl]-cyclohexanol, was was exemplified as a fumarate salt in U.S. Pat. No. 4,535,186. However, the fumarate salt of O-desmethyl-venlafaxine has unsuitable physicochemical and permeability characteristics. O-desmethyl-venlafaxine is also exemplified as a free base in International Patent Publication No. WO 00/32555.

Salt formation provides a means of altering the physicochemical and resultant biological characteristics of a drug without modifying its chemical structure. A salt form can have a dramatic influence on the properties of the drug. The selection of a suitable salt is partially dictated by yield, rate and quantity of the crystalline structure. In addition, hygroscopicity, stability, solubility and the process profile of the salt form are important considerations. The identification of a salt form that exhibits a suitable combination of properties can be difficult.

Solubility is one important characteristic of a salt form that can affect its suitability for use as a drug. Where aqueous solubility is low, i.e. less than 10 mg/ml, the dissolution rate at in vivo administration can be rate limiting in the absorption process leading to poor bioavailability. Hygroscopicity is also an important characteristic. Compounds having low hygroscopicity tend to have better stability and easier processing.

SUMMARY OF THE INVENTION

The present invention provides a novel salt of O-desmethyl-venlafaxine, O-desmethyl-venlafaxine succinate (hereinafter referred to as "ODV succinate"). The novel salt of the present invention has properties which are particularly suitable for use as a drug, including improved solubility, permeability, and bioavailability. For example, ODV succinate is well absorbed in the gastrointestinal tract. Furthermore, oral administration of ODV succinate results in a lower incidence of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus than oral administration of venlafaxine. Additionally, sustained release oral formulations of ODV succinate result in a lower incidence of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus than oral administration of venlafaxine. Pharmaceutical compositions comprising ODV succinate and pharmaceutically acceptable carriers or excipients are also provided. Preferably, the pharmaceutical compositions comprise an amount of ODV succinate effective to treat the desired indication in an animal, such as a human.

In further embodiments of the present invention are provided methods of treating patients suffering from depression (include, but not limited to, major depressive disorder, bipolar disorder, and dysthymia), anxiety, panic disorder, generalized anxiety disorder, post traumatic stress disorder, premenstrual dysphoric disorder, fibromyalgia, agorophobia, attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction (including, but not limited to, premature ejaculation), borderline personality disorder, chronic fatigue syndrome, urinary incontinence, pain (including, but not limited to, migraine, chronic back pain, phantom limb pain, central pain, neuopathic pain such as diabetic neuropathy, and postherpetic neuropathy), Shy Drager syndrome, Raynaud's syndrome, Parkinson's disease, and epilepsy comprising providing to a patient an effective amount of ODV succinate. ODV succinate can also be administered to prevent relapse or recurrence of depression, to induce cognitive enhancement, to treat cognitive impairment, and in regimens for cessation of smoking or other tobacco uses. Additionally, ODV succinate can be administered to treat hypothalamic amenorrhea in depressed and non-depressed human females. These methods include administering to a patient in need thereof, an effective amount of ODV succinate or a substantially pure polymorph of ODV succinate, or mixtures thereof.

The present invention also provides four crystalline polymorphic forms of ODV succinate (hereinafter referred to as Forms I, II, III, and IV, respectively) and an amorphous form of ODV succinate. According to a preferred embodiment, the pharmaceutical composition of the present invention comprises at least about 20, 30, 40, 50, 60, 70, 80, 90, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, or 99.9% by weight of Form I, II, III, or IV or the amorphous form of ODV succinate, based upon 100% total weight of ODV succinate in the pharmaceutical composition (or the total weight of crystalline ODV succinate in the pharmaceutical composition).

Another embodiment is a method for preparing the free base of O-desemthyl-venlafaxine by demethylating venlafaxine or a salt thereof with an alkali metal salt of a trialkylborohydride.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an X-ray powder diffractogram (XRPD) of Form I of ODV succinate prepared in Example 7.

FIG. **2** is an XRPD of Form II of ODV succinate prepared in Example 8.

FIG. **3** is an XRPD of Form III of ODV succinate prepared in Example 9.

FIG. **4** is an XRPD of Form IV of ODV succinate prepared in Example 10.

FIG. **5** is an XRPD of the amorphous form of ODV succinate prepared in Example 11.

FIG. **6** are differential scanning calorimetry (DSC) analyses of Forms I, II, and IV and the amorphous form of ODV succinate from 25 to 250° C. in hermetically-sealed pans at a scan rate of 10° C./minute under a nitrogen purge.

FIG. **7** is an XRPD of Form I of the ODV succinate prepared in Example 1.

FIG. **8** are thermogravimetric analyses (TGA) of Forms I, II, and IV and the amorphous form of ODV succinate heated from 25 to 300° C. at a scan rate of 10° C./minute under a nitrogen purge.

FIG. **9** is a graph of the rat intestinal permeability coefficient (Peff) experimentally determined in Example 14 and predicted human in vivo fraction of dose absorbed (Fa (%)) for ODV succinate, metoprolol, glucose, and mannitol.

FIG. **10** is a graph of the Peff experimentally determined and Fa calculated in Example 14 for ODV succinate absorbed in the duodenum-jejunum, ileum, and colon.

FIG. **11** is a graph of Peff experimentally determined and Fa calculated in Example 14 for ODV fumarate, metoprolol, glucose, and mannitol.

FIG. **12** is a graph of the Peff experimentally determined and Fa calculated in Example 14 for ODV fumarate absorbed in the duodenum-jejunum, ileum, and colon.

FIG. **13** is a comparison of the site specific absorption of ODV fumarate versus ODV succinate in the duodenum-jejunum, ileum, and colon in Example 14.

FIG. **14** is a reaction scheme for preparing the free base of O-desmethyl-venlafaxine from venlafaxine with L-selectride.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "about" generally means within 10%, preferably within 5%, and more preferably within 1% of a given value or range. Alternatively, the term "about" means within an acceptable standard error of the mean, when considered by one of ordinary skill in the art.

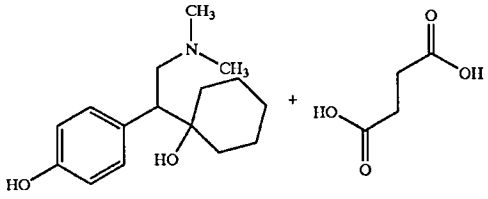
The term "monohydrate" as used herein refers to a hydrate in which one molecule of water is associated with each molecule of ODV succinate.

The term "hemihydrate" as used herein refers to a hydrate in which one molecule of water is associated with every two molecules of ODV succinate.

The term "treat" as used herein refers to preventing, amelliorating, controlling, or curing the desired symptoms or disorders.

The term "substantially the same" when used to describe X-ray powder deffraction patterns, is meant to include patterns in which peaks are within a standard deviation of ±0.2° 2θ.

The present invention relates to a novel salt of O-desmethyl-venlafaxine, O-desmethyl-venlafaxine succinate (hereinafter referred to as "ODV succinate"). ODV succinate provides optimal properties for formulation due to its high solubility, permeability, and bioavailability, and has the structural formula:



Succinic acid salts of O-desmethyl-venlafaxine exist as enantiomers and this invention includes racemic mixtures as well as stereoisomerically pure forms of the same. The term "ODV succinate" as used herein refers to racemic mixtures and stereoisomerically pure forms of ODV succinate, unless otherwise indicated.

The term "stereoisomerically pure" refers to compounds which are comprised of a greater proportion of the desired isomer than of the optical antipode. A stereoisomerically pure compound is generally made up of at least about 90% of the desired isomer, based upon 100% total weight of ODV succinate.

Succinic acid is a dicarboxylic acid and the invention therefore includes both salts in which the ratio of O-desmethyl-venlafaxine to acid (by mole) is 1:1 (i.e., a monosuccinate) and salts in which the ratio of O-desmethyl-venlafaxine to acid (by mole) is 2:1 (i.e., a bis isuccinate), as well as mixed salts, with for example an alkali metal or ammonium cation. The invention also includes mixtures of ODV succinate and the free base of O-desmethyl-venlafaxine. The crystalline polymorphs (i.e. Forms I, II, III, and IV) and the amorphous form of ODV succinate discussed below are monosuccinate salts, i.e., the molar ratio of O-desmethyl-venlafaxine to acid is 1:1. Salts of the present invention can be crystalline and may exist as more than one polymorph. Each polymorph forms another aspect of the invention. Hydrates as well as anhydrous forms of the salt are also encompassed by the invention. In particular the monohydrate form of O-desmethyl venlafaxine succinate is preferred.

ODV succinate generally has a solubility in water of greater than 30 mg/mL. Preferably, the aqueous solubility of the ODV succinate is at least 25, 30, 32, 35, 40, or 45 mg/mL at 25° C.

Succinic acid salts may be formed by contacting stoichiometric amounts of the acid with O-desmethy-venlafaxine free base. Alternatively, the acid may be used in excess, usually no more than 1.5 equivalents. Preferably the base and/or the acid are in solution, more preferably both are in solution.

The crystalline salt may be prepared by directly crystallizing from a solvent. Improved yield may be obtained by evaporation of some or all of the solvent or by crystallization at elevated temperatures followed by controlled cooling, preferably in stages. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the production process and the particle size distribution and form of the product.

Form I

Crystalline polymorph Form I of ODV succinate is a monohydrate and is stable at room temperature. Form I is physically stable up to at least about 105° C. and at 5–95% relative humidity. According to differential scanning calorimetry (DSC), Form I has an endotherm at about 131° C. (see FIG. **6**). Form I of ODV succinate has an XRPD pattern substantially identical to that shown in FIGS. **1** (ground Form I) and **7** (unground Form I). Peak locations and intensities for the XRPD pattern in FIG. **1** are provided in Table 1 below.

TABLE 1

Characteristic XRPD Peaks (expressed in degrees 2θ ± 0.2° 2θ) and Relative Intensities of Diffraction Lines for Form I of ODV Succinate

Degrees 2θ ± 0.2° 2θ	I/I_1
10.20	17
14.91	12
20.56	18
22.13	11
23.71	13
24.60	14
25.79	100

In particular, the peaks (expressed in degrees 2θ±0.2° 2θ) at 10.20, 14.91, 20.56, 22.13, 23.71, 24.60, and 25.79 are characteristic of Form I.

Form I may be prepared from the free base of O-desmethyl-venlafaxine as follows. The free base of

O-desmethyl-venlafaxine and succinic acid are dissolved in aqueous acetone. The resulting solution may optionally be filtered to remove any byproducts, such as those produced during the preparation of the free base of O-desmethyl-venlafaxine. The solution is then slowly cooled (e.g., for 3 hours or longer) to yield Form I of ODV succinate. The crystals of Form I may be recovered by any method known in the art.

Form I can also be prepared by preparing a slurry containing (a) Form I and (b) Form II, Form III, or a mixture thereof with (c) acetone, acetonitrile, a mixture of acetonitrile and water (e.g., a 9:1 mixture), or a mixture of ethanol and toluene (e.g., a 1:1 mixture) at ambient temperature.

Any crystals prepared by the aforementioned methods may be recovered by technique known to those silled in the art, such as, for example, filtration.

Form II

Crystalline polymorph Form II of ODV succinate is a monohydrate and is more thermally stable than Form III. According to DSC, Form II has an endotherm at about 127° C. (see FIG. 6). Form II of ODV succinate has an XRPD pattern substantially identical to that shown in FIG. 2. Peak locations and intensities for the XRPD pattern in FIG. 2 are provided in Table 2 below.

TABLE 2

Characteristic XRPD Peaks (expressed in degrees 2θ ± 0.2° 2θ) and Relative Intensities of Diffraction Lines for Form II of ODV Succinate

Degrees 2θ ± 0.2° 2θ	I/I_1
10.25	22
13.18	14
14.04	10
14.35	35
14.66	18
16.68	52
17.67	29
19.24	29
20.38	16
20.56	25
23.41	24
23.78	16
24.57	13
25.13	10
25.80	100
31.78	14

In particular, the peaks (expressed in degrees 2θ±0.2° 2θ) at 13.18, 14.04, 14.35, 14.66, 16.68, 17.67, 19.24, 25.13, and 31.78 are characteristic of Form II.

Form II can be prepared by rotary evaporation of Form I dissolved in acetone.

Form II can also be prepared by slow cooling of either saturated acetone or 95:5 ethanol:water solutions of Form I of ODV succinate. According to one embodiment, slow cooling is performed as follows. A mixture of the solvent and Form I of ODV succinate is prepared and heated and stirred on a hotplate (preferably set at 60–75° C.). Solvent is added until the ODV succinate is nearly all dissolved. The resulting mixture is optionally filtered (e.g., through a 0.2-μm nylon filter) into a clean vial pre-warmed, preferably on the same hotplate. The heat source is turned off, and the hotplate and vial are allowed to cool to ambient temperature. The vial is then allowed to stand at ambient temperature overnight. If no solids are generated, the vial is placed in a refrigerator for at least one day. Again, if no solids are generated, the vial is placed in a freezer for at least one day. Any solids are removed by vacuum filtration and allowed to air dry. In cases where no solid is obtained, a portion of the solvent is allowed to evaporate, and the procedure is repeated with heating and filtering.

Yet another method for preparing Form II is by precipitating Form I of ODV succinate from a solvent/anti-solvent mixture of ethanol/hexanes. Suitable solvents include those in which ODV succinate has a solubility of greater than 1 mg/mL. Suitable anti-solvents include those in which ODV succinate has low solubility, e.g., a solubility of less than 1 mg/mL. According to one embodiment, the solvent is saturated with ODV succinate. The mixture is heated, if necessary, to dissolve the ODV succinate. The mixture is filtered (e.g., through a 0.2-μm nylon filter) into a vial of cold anti-solvent (e.g., a solvent in which ODV succinate has a solubility of less than 0.1%). The resulting mixture may be placed in a freezer to increase the yield.

Form II can be prepared by slow evaporation of Form I of ODV succinate from water. For example, Form I of ODV succinate may be dissolved in water and then left in a perforated container at ambient temperature to form crystalline polymorph Form II.

Form II can be prepared by fast evaporation of Form I of ODV succinate from acetonitrile or ethanol/hexanes or ethanol/chloroform mother liquors. For example, Form I of ODV succinate may be dissolved in the solvent and then left in an open container at ambient temperature to form crystalline polymorph Form II.

Form II can be prepared by rapid cooling of an aqueous or aqueous/acetone solution of ODV succinate. Rapid cooling can be performed by any method known in the art, such as, for example, by applying a vacuum and/or an ice or ice/water bath.

Form II can also be prepared by subjecting the amorphous form of ODV succinate to 75% or greater relative humidity (e.g., at room temperature).

Any crystals prepared by the aforementioned methods may be recovered by known techniques.

Form III

Crystalline polymorph Form III of ODV succinate is a hydrate. The molar ratio of water to ODV succinate is less than 1 but more than ½ (i.e., Form III of ODV succinate is between a hemihydrate and a monohydrate). Form III of ODV succinate has an XRPD pattern substantially identical to that shown in FIG. 3. Peak locations and intensities for the XRPD pattern in FIG. 3 are provided in Table 3 below.

TABLE 3

Characteristic XRPD Peaks (expressed in degrees 2θ ± 0.2° 2θ) and Relative Intensities of Diffraction Lines for Form III of ODV Succinate

Degrees 2θ ± 0.2° 2θ	I/I_1
10.36	23
13.74	11
14.40	20
14.68	18
14.96	16
16.75	49
17.48	17
17.76	17
19.26	24
20.42	13
20.74	20
22.55	11
23.58	16
23.82	20
24.92	12
26.00	100
31.86	17
32.42	10

In particular, the peaks (expressed in degrees 2θ±0.2° 2θ) at about 13.74, 22.55, and 32.42 are characteristic of Form III.

Form III can be prepared by ball milling or cryo-grinding Form I of ODV succinate. Ball milling is performed by placing a ball in a cylinder with the ODV succinate and then shaking the cylinder. Cryo-grinding is performed by placing the ODV succinate in a cylinder and shaking the cylinder while maintaining the temperature of the cylinder at cryogenic temperatures (e.g., at <−90° C.).

Any crystals prepared by the aforementioned methods may be recovered by any known technique.

Form IV

Crystalline polymorph Form IV of ODV succinate is anhydrous. According to DSC, Form IV has an endotherm at about 145° C. (see FIG. 6). Form IV of ODV succinate has an XRPD pattern substantially identical to that shown in FIG. 4. Peak locations and intensities for the XRPD pattern in FIG. 4 are provided in Table 4 below.

TABLE 4

Characteristic XRPD Peaks (expressed in degrees 2θ ± 0.2° 2θ) and Relative Intensities of Diffraction Lines for Form IV of ODV Succinate

Degrees 2θ ± 0.2° 2θ	I/I_1
10.46	36
11.29	15
13.69	10
14.48	60
15.17	18
16.62	74
17.22	14
17.61	42
19.22	10
19.64	48
20.91	83
21.61	33
22.55	12
23.84	89
24.77	21
25.34	15
25.92	21
26.40	100
28.86	24
29.80	12
30.60	21
33.17	10
36.85	21
37.70	12

In particular, the peaks (expressed in degrees 2θ±0.2° 2θ) at about 11.29, 17.22, 19.64, 20.91, 21.61, 28.86, 29.80, 30.60, 36.85, and 37.70 are characteristic of Form IV.

Form IV can be prepared by slurrying equal amounts of Form I and Form II in acetonitrile at about 54° C. for several days (e.g., eight days), filtering, and heating the resulting solid for 18 hours at about 120° C. The crystals can be recovered by any method known in the art.

Amorphous Form

The amorphous form of ODV succinate has an XRPD pattern substantially identical to that shown in FIG. 5. FIG. 5 shows an amorphous form of ODV succinate. The glass transition (T_g) onset for the amorphous form occurs at 18° C. According to DSC, the amorphous form undergoes a major endotherm at about 120° C. (see FIG. 6). Without being bound by any theory, the inventors believe that the amorphous form was converted into a crystalline form before reaching 120° C., since amorphous forms typically do not exhibit endotherms, while crystalline forms do.

The amorphous form can be produced by forming a melt by heating Forms I, II, III, or IV, or a mixture thereof and cooling the melt to form a glass. For example, the amorphous form can be prepared by holding Forms I, II, III, or IV or a mixture thereof at about 150° C. for about 6 to about 18 minutes to form a melt and then cooling the melt to form a glass. The cooling can be done slowly or rapidly (e.g., by crash cooling).

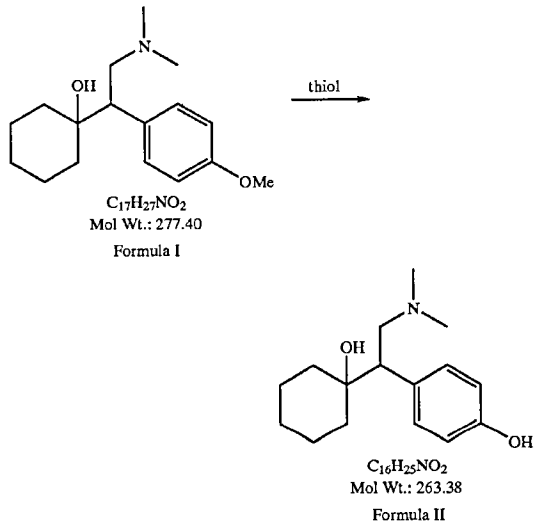
The amorphous form can be converted to Form II by placing the amorphous material in a high relative humidity environment (e.g., greater than about 50 or about 75% relative humidity).

Preparation of ODV Free Base

O-desmethyl-venlafaxine (ODV) free base may be prepared according to the general procedures outlined in U.S. Pat. No. 4,535,186.

Another method of preparing ODV free base is by demethylating a compound of Formula I (venlafaxine) to provide a compound of Formula II as described in Scheme I below.

Scheme I



$C_{17}H_{27}NO_2$
Mol Wt.: 277.40
Formula I

$C_{16}H_{25}NO_2$
Mol Wt.: 263.38
Formula II

As described in Scheme I the starting material, venlafaxine (Formula I), is demethylated. Venlafaxine may be prepared in accordance with procedures known in the art, such as those described in U.S. Pat. No. 4,535,186, which is herein incorporated by reference.

Demethylation is performed using a high molecular weight alkane, arene, or arylalkyl thiolate anion, such as straight or branched chain alkane thiolate anions having 8 to 20 carbon atoms, mono or bicyclic arene thiolate anions having 6 to 10 carbon atoms, or mono or bicyclic arylalkyl thiolate anions having 7 to 12 carbon atoms in the presence of a protic or aprotic solvent. Optionally, a base such as an alkoxide comprised of a straight or branched chain alkyl group of from 1 to 6 carbon atoms may be present to generate the thiolate anion.

Preferably the aliphatic thiol has from 10 to 20 carbon atoms and most preferably the aliphatic thiol is dodecanethiol. The aromatic thiol is preferably benzenethiol. The arylalkyl thiolate anion is preferably toluenethiol or naphthylmethanethiol.

When present, the alkoxide is preferably a lower alkoxide (methoxide, ethoxide and the like) such as sodium methoxide (sodium methylate, sodium methanolate).

The solvent is preferably a hydroxylic or ethereal solvent, and more preferably an alcohol, ethylene glycol or ether of ethylene glycol. Ethers of ethylene glycol include, but are

not limited to, ethyleneglycol monoethylether, triethyleneglycoldimethylether and polyethylene glycol. Preferably, the solvent is an inert, polar, high boiling point ether of ethylene glycol such as polyethylene glycol and most preferably PEG 400 (polyethylene glycol having a molecular weight range of from about 380–420).

The reaction is performed at a temperature of from about 150° C. to about 220° C., more preferably from about 170° C. to about 220° C., and most preferably from about 180° C. to about 200° C. The reaction is generally allowed to progress until, ideally, not more than 1% venlafaxine remains. In some aspects of the invention the reaction is complete in from about 2 hours to about 5 hours and more preferably in from about 2 to about 3.5 hours.

In preferred embodiments of this method, venlafaxine base is dissolved in polyethylene glycol 400 containing dodecanethiol and sodium methylate as a solution in methanol as the temperature is increased to from about 180° C. to about 200° C., with stirring for about 2 to about 3.5 hours.

Thereafter the reaction mixture is cooled to between about 65° C. and about 75° C. and an alcohol may be added as a diluent before neutralization to the isoelectric point (about pH 9.5 to about pH 10.0) with an appropriate neutralization agent such as hydrochloric acid. The alcoholic medium may also aid in the crystallization of the product as neutralization is initiated.

Preferably the alcohol comprises a straight or branched chain alkyl group of 1 to 6 carbon atoms, such as methanol, ethanol, isopropanol, butanol, and the like, and mixtures thereof. In some preferred embodiments of this method, the alcohol is isopropanol.

Yields of this method are greater than about 75% and generally from about 85% to greater than 90%.

Yet another method of preparing ODV free base is by demethylating venlafaxine or a salt thereof (e.g., a non-reducible salt of venlafaxine, such as the hydrochloride salt) with an alkali metal salt of a trialkylborohydride. The alkyl groups in trialkylorohydride can independently be C_1–C_6 alkyl and preferably are independently C_1–C_4 alkyl. The alkyl substituents on the trialkylborohydride can be the same or different. Suitable alkali metals include, but are not limited to, lithium, sodium, and potassium. Suitable trialkylborohydrides include, but are not limited to, selectride (tri-sec-butylborohydride) or triethylborohydride. Non-limiting examples of suitable salts include L-selectride, K-selectride, lithium triethylborohydride, and potassium triethylborohydride. Preferred salts include, but are not limited to, L-selectride and lithium triethylborohydride. A more preferred salt is L-selectride.

Generally, the demethylation process is performed in one or more of the following solvents: 1,2-dimethoxyethane, tetrahydrofuran (THF), 1,2-dethoxyethane and diglyme (bis (2-methoxyethyl) ether). The reaction is typically performed at or less than the boiling point of the solvent. Preferably, the reaction is performed at a temperature of from about 60 to about 140° C., more preferably from about 80 to about 100° C., and even more preferably from about 85 to about 95° C. The reaction is generally performed until the majority of venlafaxine has been demethylated and preferably until at least 80, 90, 95, or 99% of the venlafaxine has been demethylated. Broadly, the reaction is performed for from about 8 to about 48 hours. According to one embodiment, the reaction is performed for from about 12 to about 36 hours and preferably for about 24 hours.

The reaction results in an alkali metal salt of O-desmethyl-venlafaxine. The alkali metal salt can be converted to its free base by methods known in the art, such as neutralization with acid (e.g., to the isoelectric point).

This process for demethylating venlafaxine does not change the optical activity of the venlafaxine starting material. In other words, if the starting material is a racemic mixture of venlafaxine, the product of this demethylation process will also be a racemic mixture. If the starting material is an optically pure enantiomer, the product of this demethylation process will also be the same optically pure enantiomer.

An example of this reaction scheme for producing O-desmethyl-venlafaxine free base is shown in FIG. 14.

This process for demethylating venlafaxine can produce the free base of ODV in substantially pure form (e.g., with <0.5, 0.4, 0.3, 0.2, 0.1, 0.09, 0.08, 0.07, 0.06, or 0.05% of impurities (w/w) (excluding inorganics) as measured by HPLC).

Demethylation with a trialkylaborohydride produces various hazardous boron containing byproducts. For example, use of L-selectride results in the formation of tris(1-methylpropyl)borane and tris(1-methylpropyl)boroxin as byproducts. These byproducts may be deactivated (or stabilized) by oxidation and, optionally, hydrolysis (of intermediate borate esters). Oxidation may be performed by reacting the boron containing byproducts with an oxidizing agent, such as hydrogen peroxide, perborates (e.g., sodium perborate), or a mixture thereof. A preferred oxidizing agent is an alkaline perborate solution (e.g., an aqueous solution containing sodium hydroxide and sodium perborate tetrahydrate). Preferably, the boron containing byproducts are added to the oxidizing agent or a solution comprising the oxidizing agent.

As described in Reviews in Contemporary Pharmacology, Volume 9(5) page 293–302 (1998), incorporated by reference in its entirety, O-desmethyl-venlafaxine has the following pharmacological profile shown in Table 5 below.

TABLE 5

	O-desmethylvenlafaxine
Effect (in vivo)	
Reversal of Reserpine-Induce Hypothermia (minimum effect; mg/kg i.p.)	3
Effect (in vitro)	
Inhibition of amine reuptake (IC50; uM)	
Norepinephrine	1.16
Serotonin	0.18
Dopamine	13.4
Affinity for Various Neuroreceptors (% inhibition at 1 uM)	
D2	6
Cholinergic	7
Adrenergic α	0
Histamine H1	0
Opiate	7

Thus, compounds, compositions and methods of the present invention can be used to treat or prevent central nervous system disorders including, but not limited to depression (including but not limited to major depressive disorder, bipolar disorder and dysthymia), fibromyalgia, anxiety, panic disorder, agorophobia, post traumatic stress disorder, premenstrual dysphoric disorder (also known as premenstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol

addiction, sexual dysfunction, (including premature ejaculation), borderline personality disorder, chronic fatigue syndrome, incontinence (including fecal incontinence, overflow incontinence, passive incontinence, reflex incontinence, stress urinary incontinence, urge incontinence, urinary exertional incontinence and urinary incontinence), pain (including but not limited to migraine, chronic back pain, phantom limb pain, central pain, neuropathic pain such as diabetic neuropathy, and postherpetic neuropathy), Shy Drager syndrome, Raynaud's syndrome, Parkinson's Disease, epilepsy, and others. Compounds and compositions of the present invention can also be used for preventing relapse or recurrence of depression; to treat cognitive impairment; for the inducement of cognitive enhancement in patient suffering from senile dementia, Alzheimer's disease, memory loss, amnesia and amnesia syndrome; and in regimens for cessation of smoking or other tobacco uses. Additionally, compounds and compositions of the present invention can be used for treating hypothalamic amenorrhea in depressed and non-depressed human females.

In some preferred embodiments of the invention, O-desmethyl-venlafaxine succinate is useful for the treatment of depression, anxiety, panic disorder, generalized anxiety disorder, post traumatic stress and premenstrual dysphoric disorder.

This invention provides methods of treating, preventing, inhibiting or alleviating each of the maladies listed above in a mammal, preferably in a human, the methods comprising administering an effective amount of a compound of the invention to a mammal in need thereof. An effective amount is an amount sufficient to prevent, inhibit, or alleviate one or more symptoms of the aforementioned conditions.

The dosage amount useful to treat, prevent, inhibit or alleviate each of the aforementioned conditions will vary with the severity of the condition to be treated and the route of administration. The dose, and dose frequency will also vary according to age, body weight, response and past medical history of the individual human patient. In generally the recommended daily dose range for the conditions described herein lie within the range of 10 mg to about 1000 mg O-desmethylvenlafaxine per day and more preferably within the range of about 15 mg to about 350 mg/day and still more preferably from about 15 mg to about 140 mg/day. In other embodiments of the invention the dosage will range from about 30 mg to about 90 mg/day. Dosage is described in terms of the free base and is adjusted accordingly for the succinate salt. In managing the patient, is generally preferred that the therapy be initiated at a lower dose and increased if necessary. Dosages for non-human patients can be adjusted accordingly by one skilled in the art.

Another embodiment of the invention is a method of lowering the incidence of nauseau, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus resulting from the oral administration of venlafaxine, O-desmethylvenlafaxine, or a salt of O-desmethylvenlafaxine other than O-desmethylvenlafaxine succinate to a patient. The method includes orally administering to a patient in need thereof a therapeutically effective amount of O-desmethylvenlafaxine succinate.

Yet another embodiment of the invention is a method of lowering the incidence of nauseauu, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus resulting from the oral administration of O-desmethylvenlafaxine succinate to a patient. The method includes orally administering to a patient in need thereof a therapeutically effective amount of a sustained release oral dosage form comprising O-desmethyl-venlafaxine succinate having a peak blood plasma level of less than about 225 ng/ml.

O-desmethylvenlafaxine succinate may also be provided in combination with venlafaxine. The dosage of venlafaxine is preferably about 75 mg to about 350 mg/day and more preferably about 75 mg to about 225 mg/day. Still more preferably the dosage of venlafaxine is about 75 mg to about 150 mg/day. The ratio of O-desmethylvenlafaxine to venlafaxine will vary from patient to patient depending upon a patient's response rate, but generally will be at least 6:1 O-desmethylvenlafaxine to venlafaxine.

Any suitable route of administration can be employed for providing the patient with an effective amount of O-desmethylvenlafaxine succinate. For example, oral, mucosal (e.g. nasal, sublingual, buccal, rectal or vaginal), parental (e.g. intravenous or intramuscular), transdermal, and subcutaneous routes can be employed. Preferred routes of administration include oral, transdermal and mucosal.

O-desmethyl venlafaxine succinate can be combined with a pharmaceutical carrier or excipient (e.g., pharmaceutically acceptable carriers and excipients) according to conventional pharmaceutical compounding technique to form a pharmaceutical composition or dosage form. Suitable pharmaceutically acceptable carriers and excipients include, but are not limited to, those described in Remington's, *The Science and Practice of Pharmacy*, (Gennaro, A. R., ed., 19th edition, 1995, Mack Pub. Co.) which is herein incorporated by reference. The phrase "pharmaceutically acceptable" refers to additives or compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to an animal, such as a mammal (e.g., a human). For oral liquid pharmaceutical compositions, pharmaceutical carriers and excipients can include, but are not limited to water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like. Oral solid pharmaceutical compositions may include, but are not limited to starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders and disintegrating agents. The pharmaceutical composition and dosage form may also include venlafaxine or a salt thereof as discussed above.

According to one embodiment, the majority of ODV succinate particles in a pharmaceutical composition or dosage form of the present invention have a particle size between 45 and 400 microns. Preferably, more than 60 or 65% of the particles have a particle size between 45 and 400 microns.

Dosage forms include, but are not limited to tablets, capsules, troches, lozenges, dispersions, suspensions, suppositories, ointments, cataplasms, pastes, powders, creams, solutions, capsules (including encapsulated spheroids), and patches. The dosage forms may also include immediate release as well as formulations adapted for controlled, sustained, extended, or delayed release. Most preferably tablets and capsules are the dosage form. Tablets and spheroids may be coated by standard aqueous and nonaqueous techniques as required.

Each dosage form generally contains from about 15 to about 350 mg of ODV succinate (as measured by the free base equivalent). More preferably, each dosage form contains from about 30 to about 200 mg of ODV succinate (as measured by the free base equivalent) and even more preferably from about 75 to about 150 mg of ODV succinate (as measured by the free base equivalent).

According to one preferred embodiment, the pharmaceutical composition is an extended release formulation, such as

that described in U.S. Pat. No. 6,274,171, which is herein incorporated by reference. For example, an extended release formulation may comprise spheroids comprised of ODV succinate, microcrystalline cellulose, and, optionally, hydroxypropylmethylcellulose. The spheroids are preferably coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

According to another preferred embodiment, the pharmaceutical composition is a sustained release formulation (e.g., in the form of a tablet). The sustained release formulation may comprise ODV succinate, a rate controlling polymer material (i.e., a material which controls the rate at which the ODV succinate is released), and, optionally, other adjuvants. Suitable rate controlling polymer materials include, but are not limited to, hydroxyalkyl cellulose, such as hydroxypropyl cellulose and hydroxypropyl methyl cellulose (HPMC); poly(ethylene) oxide; alkyl cellulose, such as ethyl cellulose and methyl cellulose; carboxymethyl cellulose; hydrophilic cellulose derivatives; and polyethylene glycol. The sustained release formulation comprises from about 30 w/w to about 50% w/w of ODV succinate and from about 25 w/w to about 70% w/w of a rate controlling polymer material. Optionally, the sustained release formulation may further comprise from about 0.5 w/w to about 10% w/w and preferably from about 2 w/w to about 10% of microcrystalline cellulose. A preferred sustained release formulation comprises from about 32 w/w to about 44% w/w of ODV succinate and from about 45 w/w to about 66% w/w of hydroxyprpopyl methylcellulose. Typically, the sustained release formulation provides sustained therapeutically effective plasma levels over at least a 16 or 20 hour period. The peak serum levels during the 16 or 20 hour period are generally up to 150 ng/ml. The sustained release formulation also shows a reduced level of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus.

The following examples are illustrative but are not meant to be limiting of the present invention.

EXAMPLE 1

Preparation of Form I of ODV Succinate

Acetone (2111 mL), water (667 mL) and O-desmethylvenlafaxine (250.0 g, 0.949 mol) were mixed to form a thick white suspension which was stirred at 23° C. for 0.5 hour. Succinic acid (115.5 g, 0.978 mol) was added with acetone (236 mL) and water (75 mL). The suspension was heated to 58° C. and stirred at this temperature for 30 minutes. The reaction mixture was filtered and allowed to cool to 30–34° C. The suspension was stirred at 30–31° C. for 3 hours then cooled to 0–5° C. and stirred at this temperature for a further hour. The solids were isolated by filtration and the wet cake dried at 30° C. for 12 hours (50 mm Hg) then 40° C. for 24 hours (50 mm Hg) to afford O-des-methyl-Venlafaxine succinate monohydrate as white crystals (325.5 g, 85.7%).

mp: 122.3 C and 139.6 C

^{1}H NMR (300 MHz, DMSO-d_6) 10–9 (bs, 2H), 7.00 (d, J=8.2 Hz, 2H), 6.65 (d, J=8.2 Hz, 2H), 3.4–3.2 (bs, 1H), 3.12 (dd, J=7.0, 12.2 Hz, 1H), 2.74 (t, J=8.7 Hz, 1H), 2.7–2.58 (m, 1H), 2.50 (s, 3H), 2.36 (s, 3H), 2.28 (s, 4H), 1.50–1.25 (m, 6H), 1.20–0.80 (4H). 99.40% Purity (by HPLC).

An XRPD pattern for the (unground) crystals prepared is shown in FIG. 7. Characteristic XRPD peaks are shown in Table 6 below.

TABLE 6

X-ray powder diffractogram (CuK2α)	
Angle (° 2θ)	Relative Intensity
5.285	30.6
10.435	54.6
20.680	10.4
20.850	23.2
25.660	6.6
25.955	55.5
26.125	100.0

The crystals of Form I examined in FIG. 7 were not ground, while those in FIG. 1 were ground before being examined. Without being bound by any theory, the inventors theorize that the XRPD for the unground crystals differed from that of the ground crystals due to the preferred orientation of the unground crystals.

Bulk Density: 0.369 gms/mL

Solubility in water: 32.2 mg/ml at 25° C.

The aqueous solubility (reported above) of Form I of ODV succinate was determined according to the following procedure.

Materials

Spectrophotometer—Capable of isolating a bandwidth of 2 nm or less at the wavelength of maximum absorbance, and of measuring absorbances in the 0.0 to 1.0 range with a precision of 0.01. A Cary Model 219 spectrophotometer or equivalent is suitable.

Cells—Silica, 1 cm.

Filters—0.45 micron Nylon filters which are chemical resistant or equivalent

Bottles—Glass screw top bottles having a 15 mL or greater capacity.

Shaker—A lateral shaker, wrist shaker, or a vibrator which will not generate heat is suitable.

Sample Preparation

A. For Non UV Absorbing Solvents

1. To a bottle weigh an amount of sample equivalent to approximately 1½ times the solubility.
2. Pipet 10.0 mL of water into the bottle and secure cap tightly.
3. Agitate the bottles at ambient room temperature for at least 16 hours.
4. Obtain a clear filtrate layer by either centrifugation ot filtration being careful to avoid evaporation.
5. Quantitatively transfer the solution to a volumetric flask and dilute to volume with water.
6. Blank the instrument for water.
7. Make quantitative dilutions to arrive at a suitable concentration for measurement.

B. For UV Absorbing Solvents

1. To a bottle, weigh an amount of sample equivalent to approximately 1½ times the solubility.
2. Pipet 10.0 mL of water into the bottle and secure a cap tightly.
3. Agitate the bottles at ambient room temperature for at least 16 hours.
4. Obtain a clear filtrate layer by either centrifugation or filtration being careful to avoid evaporation.
5. Evaporate an accurate amount of solvent on a steam bath and redissolve the residue, in the solvent used to prepare the standard. Quantitatively transfer to a volumetric flask with the same solvent used in preparing the standard solution.
6. Make dilutions as necessary to obtain a concentration suitable for quantitative measurement.

Procedure

1. Obtain the spectra of the sample and standard preparations between 350 and 200 nm, using water as the blank. The wavelength range may be varied depending upon the UV cut off of water.

2. Calculate the aqueous solubility with the following equation:

$$mg/mL = \frac{(As)(Ds)(Wg - Wt)(S)}{(Ar)(Dr)(V)}$$

where

As=absorbance of the sample preparation

Ds-=dilution factor of the sample preparation, mL

Wg=gross weight of the reference standard and container, mg

Wt=tare weight, mg

S=strength of the reference standard, decimal

Ar=absorbance of the reference standard preparation

Dr=dilution factor of the reference standard preparation, mL

V=amount of solvent evaporated, mL

EXAMPLE 2

Hard Gelatin Capsule Dosage Form

Ingredient	mg/capsule	% w/w
ODV succinate	116.7 (75 as free base)	39.5
Lactose Fast Flow	177.3	60.0
Magnesium Stearate	1.5	0.5
Total	295.5	100.0

The active ingredient is sieved and blended with the listed excipients. Suitably sized hard gelatin capsules are filled using suitable machinery and methods well known in the art. Other doses may be prepared by altering the fill weight and, if necessary, by changing the capsule size to suit.

EXAMPLE 3

Preparation of O-desmethyl-venlafaxine Free Base

Dodecanethiol (122 g), venlafaxine (111 g), and a methanolic solution of sodium methanolate (30%, 90 g) and PEG 400 are heated to 190° C. The methanol is distilled off and the solution is stirred for 2 hours at 190° C. Then the temperature is lowered, 2-propanol (450 g) is added and the pH is adjusted to 9.5 with aqueous HCl. The precipitate is collected by suction filtration, and the cake is washed with 2-propanol, toluene, 2-propanol and water. The wet O-desmethylvenlafaxine is dried in vacuo.

Yield: 87 g.

^{1}H-NMR: (Gemini 200, Varian, 200 MHz) (DMSO-d6) δ=9.11 (s, br, 1H; OH), 6.98 (d, br, J=8.4, 2H; arom.), 6.65 (d, br, J=8.4, 2H; arom.), 5.32 (s, br, 1H; OH), 3.00 (dd, J=12.3 and 8.5, 1H), 2.73 (dd, J=8.5 and 6.3, 1H), 2.36 (dd, J=12.3 and 6.3, 1H) 2.15 (s, 6H, 2×Me), 1.7–0.8 (m, 10H, c-hex).

EXAMPLE 4

Preparation of O-desmethyl-venlafaxine Free Base

Venlafaxine (5.6 g) and benzenethiol sodium salt (6.9 g) are charged to PEG 400 (25 g). The reaction mixture is heated to 160° C. for 5 hours. Then the temperature is lowered and water is added (60 g). The pH is adjusted to 3.5 with H_3PO_4. The organic by-products are removed by extraction with heptanes (25 g). The pH of the aqueous layer is then adjusted to 9.5 with aqueous ammonia. The precipitate is collected by suction filtration, re-slurried in water (100 g), isolated by suction filtration and dried in vacuo.

Yield 1 g.

^{1}H-NMR: (Gemini 200, Varian, 200 MHz) (DMSO-d6) δ=9.11 (s, br, 1H; OH), 6.98 (d, br, J=8.4, 2H; arom.), 6.65 (d, br, J=8.4, 2H; arom.), 5.32 (s, br, 1H; OH), 3.00 (dd, J=12.3 and 8.5, 1H), 2.73 (dd, J=8.5 and 6.3, 1H), 2.36 (dd, J=12.3 and 6.3, 1H) 2.15 (s, 6H, 2×Me), 1.7–0.8 (m, 10H, c-hex).

EXAMPLE 5

Preparation of O-desmethyl-venlafaxine Free Base

Dodecanethiol (69 g), venlafaxine (55 g), and an ethanolic solution of sodium ethanolate (21%, 82 g) are charged to a pressure vessel. The temperature is raised to 150° C. and the reaction mixture is stirred for 2 days. Then the temperature is lowered and the solution is filtered. The pH of the filtrate is adjusted to 9.5 with aqueous hydrogen chloride. The crystals are collected by suction filtration. The cake is washed with ethanol and dried in vacuo.

Yield: 42 g

^{1}H-NMR: (Gemini 200, Varian, 200 MHz) (DMSO-d6) δ=9.11 (s, br, 1H; OH), 6.98 (d, br, J=8.4, 2H; arom.), 6.65 (d, br, J=8.4, 2H; arom.), 5.32 (s, br, 1H; OH), 3.00 (dd, J=12.3 and 8.5, 1H), 2.73 (dd, J=8.5 and 6.3, 1H), 2.36 (dd, J=12.3 and 6.3, 1H), 2.15 (s, 6H, 2×Me), 1.7–0.8 (m, 10H, c-hex).

EXAMPLE 6

Preparation of O-desmethyl-venlafaxine Free Base

A 12 L multi-necked flask, equipped with a mechanical stirrer, a thermometer, a 1 L pressure equalizing dropping funnel, and a Claisen distillation head equipped with a downward condenser attached to a 5 L receiver with a vacuum take-off, was placed in a heating mantle. The system was purged with nitrogen and a nitrogen atmosphere was maintained. The distillation flask was charged with 4.00 L (4.00 mol, 5.55 molar excess) of 1 M L-selectride. The dropping funnel was charged with a solution of 200.00 g (0.720 mol) of venlafaxine base in 0.6936 kg (800 mL) of anhydrous 1,2-dimethoxyethane while maintaining the nitrogen atmosphere. The solution of venlafaxine base was added to the stirred L-selectride solution over a period of 15 minutes using rinses of 1,2-dimethoxyethane (2×400 mL, 2×0.3468 kg). Hydrogen was vented and bubbled through a dispersion tube into water. No significant temperature change occurred during the addition.

The dropping funnel was replaced with a similar 4 L funnel charged with 2.4276 kg (2800 mL) of anhydrous 1,2-dimethoxyethane. The system was again purged with nitrogen and a nitrogen atmosphere was maintained. The solution was heated and distilled at atmospheric pressure until the liquid level reached the 4 L mark and the reaction flask temperature was 84–85° C. While distilling, 2.4276 kg (2800 mL) of 1,2-dimethoxyethane was added dropwise at a rate which maintained the liquid level at the 4.00 L level until the temperature in the reaction flask reached 93–94° C. A crystalline precipitate was observed. The distillate was discarded.

The stirred slurry of crystals was cooled to 90° C., the stirrer was stopped, and the dropping funnel and distillation equipment was removed. The flask was then equipped with a reflux condenser fitted with a nitrogen inlet. The system was purged with nitrogen and a nitrogen atmosphere was maintained. The slurry was stirred and heated at reflux under a nitrogen atmosphere for about 19 hours. The initial temperature of the slurry at reflux was 94–96° C. and the final temperature was 97° C. Copious crystallization occurred. The slurry was cooled to room temperature.

12 L of distilled water in a 20 L Duran flask was purged with nitrogen to remove oxygen and carbon dioxide. The purging was repeated as necessary. This water is hereinafter referred to as "nitrogen purged distilled water".

The heating mantle was removed and replaced with an ice/water bath to bring the temperature of the reaction mixture to near room temperature. The flask was equipped with a 1000 mL pressure equalizing dropping funnel. The stirred reaction mixture was cooled with an ice/alcohol bath to obtain a temperature of 15–20° C. While the nitrogen atmosphere was maintained, the reaction mixture was quenched by dropwise addition of 0.296 kg (296 mL) of the nitrogen purged distilled water. The addition was controlled so as to maintain the temperature below 25° C. The temperature rose to 15–24° C. as a result of an exotherm. The mixture was stirred at ambient temperature for about 1 hour. A thick gel-like precipitate, which was formed initially, was converted into a crystalline precipitate during this period. While the reaction mixture was maintained in the nitrogen atmosphere, the flask was equipped with a Claisen distillation head, a downward condenser with a vacuum take-off and a 5 L receiving flask chilled in an ice/water bath. The stirred reaction mixture was distilled under pump vaccum (109–134 mm Hg) down to the 2.80 L mark at a distillation flask temperature of 25–38° C. The distillate was discarded. 3.00 kg (3000 mL) of nitrogen purged distilled water was added.

The stirred mixture was distilled under pump vacuum (113–187 mm Hg) down to 2.80 L at a distillation flask temperature of 35–50° C. to form a biphasic mixture. The distillate (Distillate A) was discarded by the Waste Treatment procedure described below. The warm biphasic mixture (35–40° C.) was transferred to a 4 L separatory funnel using rinses of 600 mL of nitrogen purged distilled water and 0.5296 kg (600 mL) of toluene. The two phases were mixed and then allowed to separate. A small quantity of solid at the interface was discarded. The aqueous layer was extracted consecutively with toluene (2×0.5196 kg, 2×600 mL) and heptane (0.5472 kg, 800 mL). The organic phases (Extract A) were discarded by the Waste Treatment procedure described below. A sufficient amount of nitrogen purged distilled water was added to the aqueous layer to achieve a volume of 3.60 L.

A 12 L multi-necked flask was equipped with a mechanical stirrer, a thermometer, and a condenser with a nitrogen inlet. The flask was purged with nitrogen and a nitrogen atmosphere was maintained in the flask.

The 3.60 L aqueous layer was transferred to the empty 12 L flask. The stirred solution was cooled under nitrogen to 10–15° C. with an ice/water bath. From a 1000 mL pressure equalizing dropping funnel, 410 mL of 12 N hydrochloric acid was added dropwise to the stirred solution while maintaining the temperature at 10–15° C. with the ice/water bath and until a pH of 3.5±0.2 was reached. A small precipitate was formed.

The resulting suspension was filtered through a Celite pad on polypropylene cloth in a 19 cm Buchner funnel into a 5 L multi-necked flask equipped with a mechanical stirrer, a thermometer, a condenser with a nitrogen inlet and a 1000 mL pressure equalizing dropping funnel. The filter pad was washed with 300 mL of nitrogen purged distilled water.

The filter funnel was removed. The system was flushed with nitrogen and again maintained in a nitrogen atmosphere. To the stirred solution, 76 mL of 10 N sodium hydroxide was added from the dropping funnel until a pH of 9.6±0.2 was reached. The resulting slurry of crystals was cooled to 5–10° C. and the slurry of crystals was maintained at 0–5° C. for about 1 hour.

The solid was collected on a polypropylene cloth in a 19 cm Buchner funnel. The filter cake was washed with 3×200 mL of nitrogen purged distilled water. The filtrate was discarded.

A 12 L multi-necked flask was equipped with a mechanical stirrer, a thermometer, and a condenser with a nitrogen inlet. The flask was purged with nitrogen and a nitrogen atmosphere was maintained in the flask. The flask was charged with 3000 mL of nitrogen purged distilled water and cooled to 15–20° C. with an ice/water bath. The solids collected on the polypropylene cloth were added to the stirred water in the flask and stirred at 15–20° C. until a smooth suspension was obtained (about 30 minutes).

The solid was collected on a polypropylene cloth in a 19 cm Buchner funnel using 600 mL of nitrogen purged distilled water to complete the transfer. The filter cake was washed with water (3×300 mL) and filtered. A dam was formed on top of the filter with a sheet of latex rubber and an aspirator vacuum was applied to the filter flask for about 5 hours. The white solid was dried in a vacuum oven under oil pump vacuum at 80° C. for about 18 hours. The solid was crushed and re-dried if necessary to constant weight. The yield was 90.7% (172.3 g) (HPLC Analysis: Strength or Purity (w/w): 98.8%, Impurities (excluding inorganics) (w/w): 0.046%, Ash (inorganics) (w/w): 0.14%).

Waste Treatment

The waste to be discarded contained byproducts, such as tris(1-methylpropyl)-borane and tris(1-methylpropyl)-boroxin. A 22 L or 50 L multi-necked flask was equipped with a mechanical stirrer, a thermometer, and a condenser with a nitrogen inlet. The flask was purged with nitrogen using a Firestone valve and a nitrogen atmosphere was maintained in the flask.

Distillate A and Extract A were combined in the flask to obtain a biphasic mixture (4.00 L with 400 mL of an aqueous bottom phase) under a nitrogen atmosphere. The stirrer was started and 600 mL of 10 N sodium hydroxide and 600 mL of water were added. A slurry of sodium perborate tetrahydrate (1.848 kg, 12.01 moles, ~3 equivalents per mole of tris(1-methylpropyl)borane) in 12 L of water was added in portions with ice/water cooling over about 20 minutes to maintain the temperature at 28–38° C. After the exotherm had subsided, the mixture was stirred at 22–23° C. under a nitrogen atmosphere for about 18 hours. The solid dissolved and two liquid phases remained.

The stirrer was stopped and the phases were allowed to separate. The upper phase was examined by gas chromatography/mass spectrometry to determine if any tris (1-methylpropyl)borane or tris(1-methylpropyl)boroxin was still detectable. If any was detected, 80 g (0.52 mol) of sodium perborate was added as a slurry in 400 mL of water and the solution was stirred at 22–23° C. for about 18 hours. Once tris(1-methylpropyl)borane and tris(1-methylpropyl) boroxin were no longer detectable in the upper phase, the aqueous phase was checked for its oxidizing capability (for example, due to peroxides and excess sodium perborate) with starch iodide paper.

The phases of the solution were then separated. The top organic layer was combined with other organic waste from the synthesis to be discarded. The aqueous layer was combined with other aqueous waste from the synthesis to be discarded.

The following procedures were used in the Examples 7–11 below.

X-Ray Powder Diffraction

XRPD analyses were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer using Cu Kα radiation. The instrument is equipped with a fine focus X-ray tube. The tube power and amperage were set at 40 kV and 40 mA, respectively. The divergence and scattering slits were at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a Nal scintillation detector. A theta-two theta continuous scan at 3°/min (0.4 s/0.02° step) from 2.5 to 40° 2θ was used. A silicon standard was analyzed each day to check the instrument alignment.

In cases where preferred orientation [vide infra] occurred during X-ray powder diffraction, the ODV succinate was sometimes placed between folded weighing paper, then ground with an agate pestle and re-analyzed by XRPD.

Thermogravimetric Analysis (TGA)

Thermogravimetric analysis was conduct on a TA Instruments 2950 thermogravimetric analyzer. The calibration standards were nickel and Alumel™. Approximately 8–20 mg of sample were placed in the pan, accurately weighed, and inserted into the TG furnace. The samples were heated under nitrogen at a rate of 10° C./min, up to a final temperature of 300° C. Weight derivative (%/° C.) was used to determine total weight loss between 40° C. and the temperature at which the derivative was zero (usually 150° C.). The results of TGA for Examples 8–12 below are shown in FIG. 8.

Different Scanning Calorimetry

DSC analyses were carried out on a TA Instruments differential scanning calorimeter 2920. Approximately 3–5 mg of sample was placed into a DSC pan, and the weight accurately recorded. The pan was hermetically sealed. Each sample was heated under nitrogen at a rate of 10° C./min, up to final temperature of 250° C. Indium metal was used as the calibration standard. Reported DSC temperatures are at the transition maxima. The results of DSC for Examples 8, 9, 11, and 12 below are shown in FIG. 6.

DSC Glass Transition

For studies of the glass transition temperature (T_g) of the amorphous material, the sample was heated under nitrogen at a rate of 10° C./min up to a final temperature of 250° C. The sample pan was hermetically sealed.

EXAMPLE 7

Preparation of Form I of ODV Succinate

A 5 L multi-necked flask, equipped with a stirrer, a thermometer, and a condenser, with a nitrogen inlet attached to a Firestone valve were placed in a heating mantle. The system was purged with nitrogen and a nitrogen atmosphere was maintained. 1.668 kg (2111 mL) acetone and 0.667 kg (667 mL) water were charged into the flask. The stirrer was started and 0.250 kg (0.949 mol) O-desmethyl-venlafaxine free base (prepared as described in Example 6) were added. The suspension was stirred for 30 minutes. 0.1155 kg (0.978 mol) succinic acid were added and the transfer was completed with rinses of acetone (0.186 kg, 236 mL) and water (0.075 kg, 75 mL). The suspension was stirred, warmed to 60° C. (±30° C.), and maintained at 60° C. (±3° C.) while being stirred for 30–60 minutes. A clear to cloudy solution was obtained. The mixture was then filtered through a filter comprised of polypropylene cloth with a filter paper underlay into a 5 L multi-necked flask equipped with a mechanical stirrer, a thermometer, and a condenser fitted with a vacuum outlet. The filter funnel was rinsed with warm (50–60° C.) aqueous acetone (24:76 v/v, 427 mL). The system was purged with nitrogen and the solution was cooled to 30–35° C. to induce crystallization. The stirred slurry of crystals was maintained at that temperature for about 4 hours. The stirred slurry of crystals was cooled to 0–5° C. and maintained at that temperature for about 1 hour. The crystals were collected on a polypropylene cloth filter with a filter paper underlay in a 15 cm funnel. The filter cake was washed with cold (0–5° C.) aqueous acetone (24:76 v/v, 2×300 mL) and filtered for 5 minutes. A dam was formed on top of the filter with a sheet of latex rubber. An aspirator was applied to the filter cake for 1 hour. The weight of the filter cake was about 0.351 kg. The product was dried under vacuum (50 mm Hg) at 30±5° C. for 12 hours. The product was then dried under vacuum (50 mm Hg) at 45±5° C. for 24 hours.

An XRPD of the ODV succinate is shown in FIG. 1.

Alternative Preparation of Form I of ODV Succinate

A 5 L multi-necked flask equipped with a stirrer, a thermometer, and a condenser with a nitrogen inlet attached to a Firestone valve are placed in a heating mantle. The system is purged with nitrogen and a nitrogen atmosphere was maintained. 1.651 kg (2090 mL) acetone and 0.660 kg (660 mL) water are charged into the flask. The stirrer is started and 0.250 kg (0.949 mol) O-desmethyl-venlafaxine free base (prepared as described in Example 6) are added. The suspension is stirred for 30 minutes. 0.1155 kg (0.978 mol) succinic acid are added. The suspension is stirred, warmed to 60° C. (±3° C.), and maintained at 60° C. (±3° C.) while being stirred for 30–60 minutes. The mixture is then filtered through a filter comprised of Celite on polypropylene cloth with a filter paper underlay into a 5 L multi-necked flask equipped with a mechanical stirrer, a thermometer, and a condenser fitted with a vacuum outlet. The filter funnel is rinsed with warm (50–60° C.) aqueous acetone (24:76 v/v, 427 mL). The system is purged with nitrogen and the solution is cooled to 30–35° C. to induce crystallization. The stirred slurry of crystals is maintained at that temperature for about 4 hours. The stirred slurry of crystals is cooled to 0–5° C. and maintained at that temperature for about 1 hour. The crystals are collected on a polypropylene cloth filter with a filter paper underlay in a 15 cm funnel. The filter cake is washed with cold (0–5° C.) aqueous acetone (24:76 v/v, 2×300 mL) and filtered. A dam for the filter cake is formed with a sheet of latex rubber. An aspirator is applied to the filter cake for 1 hour. The weight of the wet cake is about 0.351 kg. The product is dried under vacuum (50 mm Hg) at 30±5° C. for 12 hours. The product is then dried under vacuum (50 mm Hg) at 45±5° C. for 24 hours. The yield was 85.8% (325.2 g) (HPLC Analysis: Impurities (excluding inorganics) (w/w): 0.0%, Ash (inorganics) (w/w): 0.0%, Amount of any single impurity (w/w):<0.01%).

EXAMPLE 8

Preparation of Form II of ODV Succinate

Form II was prepared by dissolving 306.1 mg of Form I in 200 ml acetone, filtering the solution through a 0.2 um

nylon disc followed by vacuum stripping the filtrate on a rotary evaporator at ambient temperature.

An XRPD of the ODV succinate is shown in FIG. 2.

EXAMPLE 9

Preparation of Form III of ODV Succinate

Form III was prepared using two different milling techniques. In the first technique, ball-mill grinding, 290.2 mg of Form I was measured into a stainless steel cylinder with a ball, the sealed container was placed on a Retsch Mixer and milled for five minutes at a frequency of 30/s. At the end of the cycle, a spatula was used to scrape material from the walls. The procedure was repeated three times for a total mill time of 20 minutes. In the second technique, cryo-grinding, 40.5 mg of Form I was charged to a stainless steel cylinder with a rod, the sealed container was then placed in a SPEX Freezer mill maintained at −96 degrees Celsius with liquid nitrogen. The material was milled for two minutes at a frequency of 10/s (20 impacts per second), then cooled for two minutes. The procedure was repeated two times for total mill time of six minutes.

An XRPD of the ODV succinate is shown in FIG. 3.

EXAMPLE 10

Preparation of Form IV of ODV Succinate

Form IV was prepared in the following manner: A mixture of equal amounts of Form I and Form II was charged to a saturated, 0.2 um-filtered solution of acetonitrile-ODV succinate at 54 degrees Celsius. The mixture was agitated for a period of eight days. The slurry was filtered and the recovered solids air-dried. The solids were then charged to a 2-dram scintillating vial and heated for eighteen hours at 120° C.

An XRPD of the ODV succinate is shown in FIG. 4.

EXAMPLE 11

Preparation of Amorphous Form of ODV Succinate

The amorphous form of ODV succinate was prepared by charging a mixture of 854.1 mg of Forms I and II to an open, 20-ml scintillating vial and then placing the vial in a 150° C. oil bath for about 18 minutes.

An XRPD of the ODV succinate is shown in FIG. 5. According to DSC, the T_g onset occurs at 18° C.

EXAMPLE 12

Preparation of Form II of ODV Succinate

56 g of O-desmethyl-venlafaxine, 26 g of succinic acid, 112 g of acetone, and 112 g of purified water were charged into a container. The resulting slurry was heated to reflux (about 62° C.) until a solution formed. The solution was cooled slightly and 1.2 g of charcoal 2S was charged. The solution was refluxed for about 15 minutes. The solution was filtered through a Seitz filter and the filter cake was washed with 5 g of acetone. The hot solution was then charged into a bulb equipped with a reflux condenser. A vacuum was applied from the top of the condenser. The solution began to boil and crystallize. The solution was stirred. The vacuum was applied until the slurry reached 20° C. The solution was cooled with an external ice bath to 5° C. The crystals were isolated by suction filtration. The filter cake was washed with a mixture of 11 g of purified water and 45 g of acetone. Air was sucked through the cake for about 2 hours. About 70 g of ODV succinate was formed.

Alternative Preparation of Form II of ODV Succinate by Fast Crystallization

A 2 L 4-neck flask was charged with O-desmethyl-venlafaxine (75.0 g, 0.285 mol), acetone (627 mL), succinic acid (34.50 g, 0.29 mol), and water (197.5 mL). The suspension was warmed to 60° C. and filtered through a pad of Celite. The filter pad was washed with a warm mixture of acetone (97 mL) and water (30.6 mL). The filtrate was transferred to a clean 2 L flask rinsing with acetone (50 mL). The temperature of the solution was 28° C. The solution was allowed to cool and crystallization began at 23° C. The mixture was then rapidly cooled in an ice/water bath to 0–5° C. The mixture was stirred at 0–5° C. for 2 hours. The solids were isolated by filtration and washed with cold aqueous acetone (2×200 mL, 25:75 v/v water/acetone). The wet filter cake was dried in a vacuum oven at 35±5° C. (50 mm Hg) for 48 hours to yield ODV succinate monohydrate as white crystals (89.5 g, 78.7%).

^{1}H NMR (300 MHz, DMSO-d_6) 10–9 (bs, 2H), 7.00 (d, J=8.2 Hz, 2H), 6.65 (d, J=8.2 Hz, 2H), 3.4–3.2 (bs, 1H), 3.12 (dd, J=7.0, 12.2 Hz, 1H), 2.74 (t, J=8.7 Hz, 1H), 2.7–2.58 (m, 1H), 2.50 (s, 3H), 2.36 (s, 3H), 2.28 (s, 4H), 1.50–1.25 (m, 6H), 1.20–0.80 (4H).

EXAMPLE 13

Rat Jejunal Test

The rat intestine perfusion technique is a direct way to measure the regional absorption properties of a test compound in the gastrointestinal tract. Rat intestinal permeability coefficient (Peff) can be used to predict human in vivo oral absorption of passively absorbed compounds. Fagerholm, M. Johansson, and H. Lennernäs, "Comparison between permeability coefficients in rat and human jejunum", *Pharm. Res.*, 13, 1996, 1336–1342, have demonstrated a good correlation between rat Peff and human fraction of dose absorbed (Fa) for a series of compounds. Meanwhile, some other characteristics such as formulable Maximum Absorbable Dose (MAD), FDA Biopharmaceutical Classification, etc. can also be estimated.

Materials

Perfusion buffer (PB) consisted of KCl (5.4 mM), NaCl (48 mM), Na_2HPO_4 (28 mM), NaH_2PO_4 (43 mM), mannitol (35 mM), polyethylene glycol (PEG)-4000 (0.1%, w/v), glucose (10 mM). The pH was adjusted to 6.8 with NaOH and osmolarity was adjusted to 290+10 mOsm/l with 1.0 M NaCl. Before the experiment, ^{14}C-PEC-4000 (0.02 μCi/mL), 3H-mannitol (0.025 μCi/mL), metoprolol (20 μg/mL), and ODV succinate or fumarate (50 μg/mL) were added.

Rats used in this study were Charles River CD males, ranging in weight from approximately 300–350 grams.

Internal Standard Compounds

Metoprolol (a well-absorbed and passively transported compound) was used as a standard and tested simultaneously along with the ODV compounds. Glucose (a well-absorbed and actively transported compound) was used to monitor the physiological functionality of the intestinal barriers. ^{14}C-labeled PEG-4000 was used as a non-absorbable marker to describe the water flux across the intestinal wall. ^{3}H-labeled mannitol was used as a paracellularly transported marker to indicate the integrity of the intestinal tight junctions.

Analytical Methods

All chemicals were of analytical grade. After each experiment, all the analytic assays were performed

promptly. For isotope determinations, 0.5 mL of perfusate sample containing ^{14}C PEG-4000 and ^{3}H-mannitol was mixed with 5 mL of scintillation cocktail. Radioactivity was counted in a liquid scintillation counter (Wallac 1409). Glucose concentration was determined by the glucose oxidase method (Biochemistry Analyzer). Metoprolol and the ODV compounds were analyzed by HPLC-UV/Vis (HP-1100 with a diode-array detector), using a YMC AQ 120 μ, 5 μ, 150×4.6 mm column and step gradient mobile phase containing water/0.1% TFA and acetonitrile. The ODV compounds and metoroplol were detected at 226 and 272 nm UV wavelength, respectively. Blank perfusate was assayed to evaluate the interference at these chromatographic conditions.

In Situ Rat Jejunal Perfusion

The perfusions were performed in three intestinal sections of anesthetized rats: duodenum-jejunum, ileum, and colon. The lengths of the segments were approximately 10–12 cm for small intestine segments and 5–6 cm for colon segments. An inflow cannula was inserted at the proximal end and an outflow cannula was inserted at the distal end. Perfusate was pumped through the segment at 0.19 mL/min, and collected at 20, 40, 55, 70, 85 and 100 minutes.

ODV succinate or fumarate was added to the perfusion working buffer at a concentration of 50 μg/mL, which is approximately equivalent to a 200 mg human does. The disappearance rates of ODV compound, metoprolol, and glucose were determined from each collection interval by comparing to the initial compound solution remaining in the syringe at the end of the 100 minutes. This is to correct for any losses due to binding to the syringe or tubing. Meanwhile, drug concentration in perfusate samples were corrected for water influx/efflux, which was computed, based on ^{14}C-PEG-4000 concentration changes.

Data Analysis

a. Recovery and Water Flux

Recovery of ^{14}C-PEG-4000 was determined to provide information on the integrity of the perfused intestinal segment:

$$\%\ PEG_{rec}=(\Sigma PEG_{out}/\Sigma PEG_{in})*100$$

Overall ^{14}C-PEG-4000 recovery was calculated and any data for which the individual recovery fell outside of the range of 96%–103% was excluded from the data set. Values below this range would indicate tissue damage that allows passage of PEG-4000 outside of the perfused segment, while values above this range would indicate significant water movement out of the segment.

Water movement across the gut wall was determined by calculation of net water fluid:

$$\text{Net Water Flux } (NWF)=[(1-PEG_{out}/PEG_{in})*Q]/L$$

where PEG_{out} and PEG_{in} are the amount of radioactivity (dpm) of ^{14}C-PEG-4000 in inlet and outlet sides of the perfused intestinal segment, respectively; Q is the flow rate of perfusate; and L is the length of perfused segment (cm).

b. Peff Calculation

The presence of the ODV compound in the perfusate was determined by HPLC. The amount of drug present at each time point was corrected for water movement across the wall of the intestine:

$$C_{out,corr}=C_{out}*(PEG_{in}/PEG_{out})$$

where C_{out} is the concentration of drug in outlet perfusate; $C_{out,corr}$ is the concentration of drug in outlet perfusate corrected for water moving in or out of the segment, as determined by the recovery of ^{14}C-PEG-4000.

Effective intestinal permeability, Peff (cm/sec), was determined by the following equation:

$$Peff=[Q*(C_{in}-C_{out,corr})/C_{in}]/2\ \pi rL$$

where Q is the flow rate; C_{in} is the concentration of drug in inlet perfusate; 2 πrL is the inner surface area of the perfused segment, with r assumed to be 0.18 cm in the rat (see G. Amidon, H. Lennernäs, V. Shah, J. Crison. "A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability." *Pharm. Res.* 12, 1995, 413–420) and L the length of the perfused segment (cm).

c. Fraction Absorbed (Fa)

The fraction of dose absorbed, Fa, in human is currently predicted from (Fagerholm, M. ibid:

$$Fa=100*(1-e^{-(2*(\alpha*Peff,rat+\beta)*(tres/r))})$$

where α and β are the correction factors, tres is the residence time in human small intestine; and r is the radius of the human small intestine.

d. Maximum Absorbable Dose (MAD)

The maximum absorbable dose, MAD, in humans can be calculated as:

$$MAD = ka * \int_0^{\infty} Cs * V * dt$$

$$MAD = ka * Cs * V_0 * tres$$

$$= (2 * Peff, h/r) * Cs * V_0 * tres$$

where ka is a first-order absorption rate constant; tres is the residence time in a human small intestine; r is the radius of the human small intestine, and V_o is the estimated volume of fluid present in the gastrointestinal tract. See Johnson, K. C., Swindell, A. C. "Guidance in setting of drug particle size specifications to minimize variability in absorption". *Pharm. Res.* 13(2), 1996, 1795–1798).

Results

Stability in Jejunal Fluids

The stability of ODV succinate or fumarate in the solutions of blank perfusion buffer (Pβ), and jejunal fluids (perfusion buffer collected by washing the isolated jejunal segment, pH=6.8) was determined at 37° C. for up to 6 hours. The results indicated than no apparent degradation/metabolism of these two salt forms was evident under these test conditions. The results for ODV Succinate are presented in Table 7 below. Similar data was obtained for ODV fumarate.

TABLE 7

Incubation Time (hours)	Blank Perfusion Buffer[1] (ODV Succinate)	Intestinal fluid[1,2] (ODV Succinate)
0	100.0	100.0
2	99.9	99.6
3	100.3	99.8
6	99.9	100.1

[1]The data is the relative percentage remaining (%) of HPLC peak area at different time points over time zero.
[2]Total protein concentration approximately 0.2 mg/ml.

Rat Jejunal Perfusion Results

Site-specific absorption of ODV succinate

The Peff values for ODV succinate in the small intestine ($0.912\pm0.067\times10-5$ cm/sec in duodenum-jejunum, $1.73\pm0.22*10^{-5}$ cm/sec in ileum) were lower than metoprolol's Peff values. The Peff value of ODV succinate in the colon was found to be $0.062\pm0.031\times10^{-5}$ cm/sec, which is about 10% of metoprolol's Peff value in the colon. The ileum segment seems to be the best absorption site for ODV

succinate. The Peff's ratio of duodenum-jejunum vs. ileum vs. colon was found to be 1.00:1.90:0.07, indicating that small intestinal sites of duodenum, jejunum, and ilcum predominate the oral absorption of this compound (μ90%) for an IR dosage form. (Dongzhou Liu, S. Ng, R. Saunders, "Effect of Polysorbate 80 on Transport of Mannitol, Glucose, and Water Flux in Rat Small Intestine", *PharmSci.*, 2, 2000; Doungzhou Liu, S. Ng, R. Saunders. "Investigating Intestinal Uptake of Zaleplon in site and Simulating/Predicting Oral Absorption in vivo", Submitted to *PharmSci.* 3(4), 2001).

Based on this experimental Peff, the human in vivo Fa of ODV succinate was predicted to be in the range of 60–77% in the small intestine and a Fa of 20% in the colon, as shown in FIGS. **9** and **10** and Table 8 below. The delivery vehicle was perfusion buffer (pH=6.8). The test at each absorption site was repeated with 3 rats and the Peff values were averaged.

TABLE 8

Rat Perfusion Data of ODV Succinate (50 μg/ml)

Absorption Site	$Peff_{ODV\ Succinate}$ (10^{-5} cm/sec)	$Peff_{Meloprolol}$ (10^{-5} cm/sec)	$Peff_{ODV\ Succinate}/Peff_{Meloprolol}$	Fa (%) (predicted human in vivo)
Jejunum	0.912 ± 0.067	2.50 ± 0.11	0.37 ± 0.04	61.3 ± 2.5
Ileum	1.73 ± 0.22	3.22 ± 0.07	0.54 ± 0.07	76.6 ± 3.8
Colon	0.062 ± 0.031	0.583 ± 0.087	0.12 ± 0.07	16.4 ± 3.4

An estimated maximum absorbable dose (MAD) was generated based on the rat data. The MAD of ODV succinate in the entire gastrointestinal (GI) tract (human) was estimated to be about 8.6 grams, which is the sum of 2236 mg in the duodenum-jejunum, 5629 mg in the ileum, and 683 mg in the colon.

Site-specific absorption of ODV fumarate

The site-specific absorption of ODV fumarate was investigated under the same study conditions as ODV succinate (50 μg/ml in pH 6.8 perfusion buffer). The test at each absorption site was repeated with 3 rats (except for in the Jejunum, where only 2 rats were tested) and the Peff values were averaged. The results are shown in Table 9 below and FIGS. **11**, **12**, and **13**.

Rat Perfusion Data of ODV Fumarate (50 μg/ml)

Absorption Site	$Peff_{ODV\ Fumarate}$ (10^{-5} cm/sec)	$Peff_{Meloprolol}$ (10^{-5} cm/sec)	$Peff_{ODV\ Fumarate}/Peff_{Meloprolol}$	Fa (%) (predicted human in vivo)
Jejunum	0.245 ± 0.237	1.78 ± 0.93	0.09 ± 0.08	30.6 ± 20.0
Ileum	0.678 ± 0.295	53	0.19 ± 0.06	44.7 ± 11.4
Colon	0	11	0	0

In general, the results show that ODV fumarate was less absorbed than ODV succinate in the rat GI tract. In the small intestine, the Peff values of the fumarate salt (0.24–0.68× 10^{-5} cm/sec) were only about 27 μ40% of the succinate's Peff values. In the colon, no measurable absorption of ODV furmarate was found.

The in vivo Fa of ODV fumarate was estimated to be in the range of 33–45% in the small intestine and 0 in the colon, indicating an overall low absorption of this compound in the entire GI tract. The MAD was predicted to be about 440 mg.

The results of the site-specific intestinal absorption of ODV succinate and ODV fumarate show that ODV succinate has better absorption in the small intestine and in the colon than ODV fumarate. Several publications have demonstrated that there is high correlation between the rat perfusion model and in vivo human absorption (see e.g., Doungzhou Liu, S. Ng, R. Saunders. "Investigating Intestinal Uptake of Zaleplon in site and Simulating/Predicting Oral Absorption in vivo", Submitted to *PharmSci.* 3(4), 2001).

EXAMPLE 14

Bioavailability of O-desmethyl-venlafaxine in Beagle Dogs

Test Formulations

An intravenous solution containing 25 mg/mL of Form I of ODV succinate was prepared by mixing 3.8168 g (2.5% w/v) of the ODV succinate in a sufficient amount of water for injection, USP to obtain 100 mL of solution.

An oral solution containing 25 mg/mL of Form I of ODV succinate was prepared by mixing 3.8170 g (2.5% w/v) of the ODV succinate in a sufficient amount of water for injection, USP to obtain 100 mL of solution. Prior to administration, the oral solution (25 mg/mL) was diluted to a concentration of 7.5 mg/mL with water.

Tablets each containing the ingredients listed in the table below were prepared by the method described in Example 15 for preparing ODV Succinate Formulation #2.

Ingredient	mg per tablet	% w/w
ODV Succinate (Form I was used in the preparation)	116.70 (75.00 as free base)	39.2
HPMC 2208 USP 100, 100 SR	175.05	58.8
Magnesium Stearate	5.95	2.0
Purified Water USP	q.s.	q.s.
Total	297.70	100.0

Capsules (HGC Size 0) each containing the ingredients listed in the table below were prepared by the method described in Example 15 for preparing ODV Succinate Formulation #1.

Ingredient	mg per tablet	% w/w
ODV Succinate (Form I was used in the preparation)	116.70 (75.00 as free base)	39.5
Microcrystalline Cellulose (Avicel PH200)*	177.26	60.0
Magnesium Stearate	1.48	0.5
Total	295.44	100.0

*Available from FMC BioPolymer of Philadelphia, PA.

Study Animals

Six male beagle dogs with body weights ranging between 10.2 and 16.0 kg were used in this study. The dogs were housed and given free access to water and food.

Study Design

The six dogs were dosed in a 4 period study. In Period 1, the dogs received 1 mL of the intravenous solution. In Period 2, the dogs received 10 mL of the oral solution. In Period 3, the dogs received the tablet. In Period 4, the dogs received the capsule. There was a one week wash out period between the first two treatment periods and a one month wash out period between treatment periods 2 and 3. Between periods 3 and 4, there was a one week wash out period. For periods 1 and 2, all dogs were fasted overnight with free access to water and fed after the four-hour bleeding. For periods 3 and 4, all dogs were fed 30 minutes prior to dosing and with free access to water.

Blood Samples

In periods 1 and 2, blood samples were drawn from the jugular vein at 0 (predose), 0.05 (intravenous only) and 0.13 (intravenous only), 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 32, and 48 hours after dosing into 5 mL heparinized vacutainers and immediately placed on ice. In periods 3 and 4, blood samples were drawn from the jugular vein at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 32 hours after dosing into 5 mL heparinized vacuatiners and immediately placed on ice. Plasma was separated in a refrigerated centrifuge and stored at −70° C. Plasma samples were then assayed.

Sample Analysis

Plasma O-desmethyl-venlafaxine concentrations were determined by the HPLC method using mass spectrometric detection described in Hicks, D. R., Wolaniuk, D., Russel, A., Cavanaugh, N., Kraml, M., "A high-performance liquid chromatographic method for the simultaneous determination of venlafaxine and O-desmethylvenlafaxine in biological fluids", *Ther. Drug Monit.* 16:100–107 (1994), which is hereby incorporated by reference. Based on a 0.2 mL sample volume, the method has a limit of quantitation for O-desmethyl-venlafaxine of 5.05 ng/mL. Total O-desmethyl-venlafaxine levels were determined after incubating 0.2 mL of plasma samples in β-glucuronidase for ~18 hours. O-desmethyl-venlafaxine-glucuronide levels were determined by subtracting the O-desmethyl-venlafaxine (separate extraction procedure without the use of β-glucuronidase and analyzed by HPLC-MS) concentrations from the total O-desmethyl-venlafaxine concentrations.

Data Analysis

Noncompartmental pharmacokinetic parameters were calculated from the individual dog plasma O-desmethyl-venlafaxine and O-desmethyl-venlafaxine-glucuronide concentration-time profiles. Area under the plasma concentration-time curves ($AUC_{0-\mu}$) values were calculated by the addition of AUC_{Last} (AUC_{Last}=the linear trapezoid rule from time zero to the last measurable plasma concentration, CP_{Last}) and CP_{Last}/lambda. The values for lambda were determined from the long-linear portion of the terminal slope of the plasma O-desmethyl-venlafaxine and O-desmethyl-venlafaxine-glucuronide concentration-time profile after the intravenous dose. The half-life (t_{half}) was calculated as t_{half}=0.693/lambda. The peak plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were noted directly from the plasma concentration-time profiles.

Absolute bioavailability was determined by comparing the dose normalized $AUC_{0-\mu}$ values following the intravenous administration.

Results

All levels reported as below limit of quantitation (BLQ) were assigned a value of zero for calculation purposes. The bioanalytical results demonstrated that O-desmethyl-venlafaxine-glucuronide levels account for the major portion of total circulating O-desmethyl-venlafaxine levels after the administration of ODV succinate.

Based on the total O-desmethyl-venlafaxine levels, the absorption of O-desmethyl-venlafaxine and ODV succinate is essentially complete from the oral formulation with 121%, 103% and 76% absolute bioavailability for the oral solution, capsule, and tablet formulations, respectively.

Mean (% CV) Bioavailability Parameters of ODV Succinate (Expressed as Free ODV Levels)

	Oral Solution (75 mg)	Capsule (75 mg)	Tablet (75 mg)	Intravenous Solution (25 mg)
AUC (ng*hr/mL)	835 (33)	904 (29)	677 (23)	746 (14)
C_{max} (ng/mL)	450 (23)	465 (37)	115 (24)	—
t_{max} (hr)	0.50 (55)	0.55 (68)	2.92 (35)	—
Absolute Bioavailability (%)	37 (25)	40 (17)	31 (24)	—

Mean (% CV) Bioavailability Parameters of ODV Succinate in Beagle Dogs Expressed as ODV-glucuronide Levels

	Oral Solution (75 mg)	Capsule (75 mg)	Tablet (75 mg)	Intravenous Solution (25 mg)
AUC (ng*hr/mL)	17349 (14)	13381 (14)	11686 (18)	4814 (11)
C_{max} (ng/mL)	3917 (33)	2633 (20)	1235 (15)	856 (20)
t_{max} (hr)	2.50 (22)	1.67 (24)	3.67 (14)	2.33 (22)
Absolute Bioavailability (%)	121 (13)	95 (9)	81 (11)	—

Mean (% CV) Bioavailability Parameters of ODV Succinate in Beagle Dogs (n = 6) Expressed as Total ODV Levels

	Oral Solution (75 mg)	Capsule (75 mg)	Tablet (75 mg)	Intravenous Solution (25 mg)
AUC (ng*hr/mL)	18184 (13)	14285 (13)	12362 (18)	5560 (9)
C_{max} (ng/mL)	4026 (32)	2841 (19)	1337 (15)	N/A

-continued

Mean (% CV) Bioavailability Parameters of ODV Succinate in Beagle Dogs (n = 6) Expressed as Total ODV Levels

	Oral Solution (75 mg)	Capsule (75 mg)	Tablet (75 mg)	Intravenous Solution (25 mg)
t_{max} (hr)	2.5 (22)	1.67 (24)	3.67 (14)	N/A
Absolute Bioavailability (%)	109 (13)	86 (7)	74 (12)	—

EXAMPLE 15

18 human subjects were given 75 mg each of Effexor® XR (venlafaxine formulation) (available from Wyeth-Ayerst Pharmaceuticals of St. Davids, Pa.), ODV succinate formulation #1, and ODV succinate formulation #2 over three different periods.

ODV succinate formulation #1, which is a capsule, is shown in the table below.

ODV Succinate Formulation #1

Ingredient	mg per tablet	% w/w
ODV Succinate (Form I was used in the preparation)	113.9 (75.00 as free base)	33.5
Lactose Fast Flow	112.2	33.0
Microcrystalline Cellulose (Avicel PH200)*	112.2	33.0
Magnesium Stearate	1.7	0.5
Purified Water	q.s.	q.s.
Total	340.0	100.0

ODV succinate formulation #1 was prepared as follows. The ODV succinate was sieved through a 400 micron screen and dry mixed with lactose and microcrystalline cellulose in a high shear mixer. The resulting mixture was wet granulated in a high shear mixer with purified water and dried in an oven or fluid bed drier. The mixture was blended with magnesium stearate and encapsulated in a capsule (HGC Size 0).

ODV succinate formulation #2, which is a tablet, is shown in the table below.

ODV Succinate Formulation #2

Ingredient	mg per tablet	% w/w
ODV Succinate (Form I was used in the preparation)	113.81 (75.00 as free base)	37.94
HPMC 2208 USP 100, 100 SR	170.44	56.81
Microcrystalline Cellulose (Avicel PH200)*	7.50	2.50
Talc	6.75	2.25
Magnesium Stearate	1.50	0.50
Purified Water	q.s.	q.s.
Total	295.44	100.0

*Available from FMC BioPolymer of Philadelphia, PA.

ODV succinate formulation #2 was prepared as follows. The ODV succinate was sieved through a 400 micron screen and dry mixed with HPMC, microcrystalline cellulose, and talc in a high sheer mixer. The mixture was then wet granulated with purified water and dried in an oven or fluid bed drier. The resulting mixture was blended with HPMC and talc. Magnesium stearate was added and the mixture was again blended. The mixture was then compressed into a tablet.

All doses were administered after subjects consumed a standardized medium-fat breakfast. Blood samples were taken 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 36, 48, and 72 hours after administration. The plasma concentrations of venlefaxine and O-desmethyl-venlafaxine in each blood sample was determined by the method described in Hicks, D. R., Wolaniuk, D., Russel, A., Cavanaugh, N., Kraml, M., "A high-performance liquid chromatographic method for the simultaneous determination of venlafaxine and O-desmethylvenlafaxine in biological fluids", *Ther. Drug Monit.* 16:100–107 (1994), which is hereby incorporated by reference.

The results are shown in the table below.

Plasma Concentrations of Venlafaxine*

Formulation	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC (ng*hr/mL)
Effexor ® XR				
Mean ± Stand. Dev.	40 ± 16	5.9 ± 0.5	9.5 ± 2.4	628 ± 265
% CV	39.9%	8.0%	25.6%	42.2%
Min–Max	11–77	4–6	4.8–13.8	139–1292

*Since ODV Succinate Formulations #1 and 2 do not include venlafaxine, the plasma concentrations of venlafaxine resulting from administration of them was zero.

Plasma Concentrations of O-desmethylvenlafaxine

Formulation	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC (ng*hr/mL)
Effexor ® XR				
Mean ± Stand. Dev.	88 ± 25	9.3 ± 2.9	13.2 ± 4.0	2430 ± 647
% CV	28.9%	31.2%	30.4%	26.6%
Min–Max	37–142	6–16	7.6–24.8	1582–3835
ODV Succinate Formulation #1				
Mean ± Stand. Dev.	282 ± 57	3.1 ± 1.3	9.4 ± 1.4	3491 ± 814
% CV	20.1%	43.0%	14.7%	23.3%
Min–Max	173–399	0.5–6	6.8–11.5	1667–5086
ODV Succinate Formulation #2				
Mean ± Stand. Dev.	135 ± 54	7.3 ± 5.5	9.3 ± 1.9	3185 ± 944
% CV	39.9%	75.4%	20.5%	29.6%
Min–Max	65–279	2–28	6.1–13.7	1100–4767

The table below shows the number of human subjects who experienced various adverse effects after administration of a singled dose of ODV Succinate Formulations #1 and 2.

Without being bound to any particular theory, it is believed that adverse effects observed with Formulation #1 are related to the peak blood plasma level and/or tmax of the formulation. By flattening the curve as in sustained release formulation, Formulation #2, the peak blood plasma level is reduced and the tmax delayed. Thus, in patients, as a flattened blood plasma concentration to time profile is achieved adverse event are reduced or eliminated. Thus, a

pharmaceutical composition comprising a sustained release formulation of ODV succinate having a peak blood plasma profile of less than about 225 ng/ml will have reduced side effects such as nausea and emesis.

Adverse Effects After Administration of a Single Dose of ODV Succinate Formulations #1 and 2

Adverse Effect	ODV Succinate Formulation #1 (n = 18)	ODV Succinate Formulation #2 (n = 18)
Nauscau (VAS > 5 mm)	10	1
Nauscau (VAS > 20 mm or spontaneous)	6	1
Vomiting	2	—
Diarrhea	1	—
Abdominal Pain	—	—
Headache	2	—
Vaso-vagal Malaise	2	—
Trismus	1	—

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

It is further to be understood that values are approximate, and are provided for description.

Patents, patent applications, publications, procedures, and the like are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties. To the extent that a conflict may exist between the specification and a reference, the language of the disclosure made herein controls.

What is claimed:

1. A compound which is O-desmethyl venlafaxine succinate.

2. The compound of claim **1**, wherein the compound is a hydrate of O-desmethyl venlafaxine succinate.

3. The compound of claim **2** which is O-desmethyl venlafaxine succinate monohydrate.

4. The compound of claim **1** wherein the salt is crystalline.

5. The compound of claim **4** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.20, 14.91, 20.56, 22.13, 23.71, 24.60, and 25.79.

6. The compound of claim **4** having an endotherm at about 131° C.

7. The compound of claim **4** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **1**.

8. The compound of claim **4** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 13.18, 14.04, 14.35, 14.66, 16.68, 17.67, 19.24, 25.13, and 31.78.

9. The compound of claim **8** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.25, 13.18, 14.04, 14.35, 14.66, 16.68, 17.67, 19.24, 20.38, 20.56, 23.41, 23.78, 24.57, 25.13, 25.80, and 31.78.

10. The compound of claim **4** having an endotherm at about 127° C.

11. The compound of claim **4** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **2**.

12. The compound of claim **4** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 13.74, 22.55, and 32.42.

13. The compound of claim **12** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.36, 13.74, 14.40, 14.68, 14.96, 16.75, 17.48, 17.76, 19.26, 20.42, 20.74, 22.55, 23.58, 23.82, 24.92, 26.00, 31.86, and 32.42.

14. The compound of claim **4** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **3**.

15. The compound of claim **4**, wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 11.29, 17.22, 19.64, 20.91, 21.61, 28.86, 29.80, 30.60, 36.85, and 37.70.

16. The compound of claim **15**, wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.46, 11.29, 13.69, 14.48, 15.17, 16.62, 17.22, 17.61, 19.22, 19.64, 20.91, 21.61, 22.55, 23.84, 24.77, 25.34, 25.92, 26.40, 28.86, 29.80, 30.60, 33.17, 36.85, and 37.70.

17. The compound of claim **4** having an endotherm at 145° C.

18. The compound of claim **4** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **4**.

19. The compound of claim **1** wherein the compound is amorphous.

20. The compound of claim **19** having a T_g onset at 18° C.

21. The compound of claim **1** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **5**.

22. The compound of claim **1** having a solubility in water of at least 30 mg/ml at about 25° C.

23. A pharmaceutical composition comprising O-desmethyl venlafaxine succinate and a pharmaceutically acceptable carrier or excipient.

24. The pharmaceutical composition of claim **23** further comprising venlafaxine.

25. A pharmaceutical dosage form comprising a therapeutically effective amount of O-desmethyl venlafaxine succinate and a pharmaceutically acceptable carrier or excipient.

26. An oral dosage form comprising a therapeutically effective amount of O-desmethyl venlafaxine succinate and a pharmaceutically acceptable carrier or excipient.

27. The oral dosage form of claim **26**, wherein the dosage form is a tablet or capsule.

28. The oral dosage form of claim **26**, wherein the oral dosage form is a sustained release formulation.

29. The oral dosage form of claim **26**, further comprising a rate controlling polymer material.

30. The oral dosage form of claim **29**, wherein the rate controlling polymer material is selected from hydroxyalkyl celluloses, poly(ethylene) oxides, alkyl celluloses, carboxymethyl celluloses, hydrophilic cellulose derivatives, and polyethylene glycol.

31. The oral dosage form of claim **29**, wherein the oral dosage form comprises from about 30 to about 50% by weight of O-desmethyl-venlafaxine succinate and from about 40 to about 70% by weight of the rate controlling polymer material, based upon 100% total weight of oral dosage form.

32. The oral dosage form of claim **31**, wherein the oral dosage form comprises from about 32 to about 44% by weight of O-desmethyl-venlafaxine succinate and from about 45 to about 66% by weight of the rate controlling polymer material, based upon 100% total weight of oral dosage form.

33. The oral dosage form of claim **26**, wherein the oral dosage form further comprises a binder.

34. The oral dosage form of claim **33**, wherein the binder is microcrystalline cellulose.

35. A method of treating a patient suffering from depression comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

36. A method of treating a patient suffering from anxiety comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

37. A method of treating a patient suffering from panic disorder comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

38. A method of treating a patient suffering from generalized anxiety disorder comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

39. A method of treating a patient suffering from post traumatic stress disorder comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

40. A method of treating a patient suffering from premenstrual dysphoric disorder comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

41. A method of treating a patient suffering from a condition selected from fibromyalgia, agorophobia, attention deficit disorder, obsessive compulsory disorder, social anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, borderline personality disorder, chronic fatigue syndrome, urinary incontinence, pain, Shy Drager syndrome, Raynaud's syndrome, Parkinson's disease, and epilepsy comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

42. A method of enhancing cognition or treating cognitive impairment in a patient comprising providing to a patient in need thereof an effective amount of O-desmethyl-venlafaxine succinate.

43. A method for cessation of smoking or other tobacco uses in a patient comprising providing to a patient in need thereof an effective amount of O-desmethyl-venlafaxine succinate.

44. A method for treating hypothalamic amenorrhea in a depressed or non-depressed human female comprising providing to a human female in need thereof an effective amount of O-desmethyl-venlafaxine succinate.

45. A method of lowering the incidence of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, or trismus resulting from the oral administration of O-desmethylvenlafaxine succinate to a patient comprising orally administering to a patient in need thereof a therapeutically effective amount of a sustained release formulation of O-desmethyl-venlafaxine succinate having a blood plasma level of no more than about 225 ng/ml.

46. A sustained release formulation comprising O-desmethyl-venlafaxine succinate and a pharmaceutically acceptable carrier or excipient, wherein the sustained release formulation provides peak serum levels of up to about 225 ng/ml.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

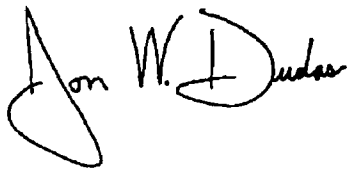
PATENT NO. : 6,673,838 B2
DATED : January 6, 2004
INVENTOR(S) : Anthony F. Hadfiedl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75], Inventors, the names of "**Michael W. Winkley**" and "**Karen W. Sutherland**" should be deleted.

Signed and Sealed this

Eighteenth Day of May, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

EXHIBIT K

Wyeth®

Effexor® XR

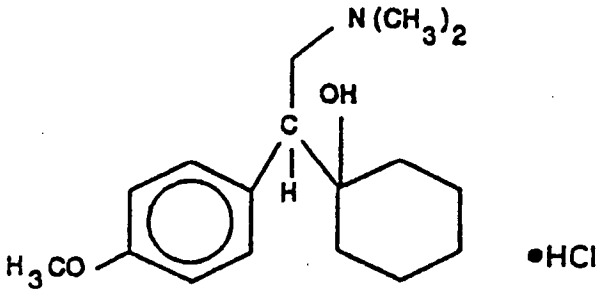
(venlafaxine hydrochloride)
Extended-Release Capsules

℞ only

This product's label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

DESCRIPTION

Effexor XR is an extended-release capsule for oral administration that contains venlafaxine hydrochloride, a structurally novel antidepressant. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ hydrochloride. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient is 0.43.

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, H_1-histaminergic, or α_1-adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics

Steady-state concentrations of venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg/day. Mean±SD steady-state plasma clearance of venlafaxine and ODV is 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; apparent elimination half-life is 5±2 and 11±2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5±3.7 and 5.7±1.8 L/kg, respectively. Venlafaxine and ODV are minimally bound at therapeutic concentrations to plasma proteins (27% and 30%, respectively).

Absorption

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.

Administration of Effexor XR (150 mg q24 hours) generally resulted in lower C_{max} (150 ng/mL for venlafaxine and 260 ng/mL for ODV) and later T_{max} (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate release venlafaxine tablets (C_{max}'s for immediate release 75 mg q12 hours were 225 ng/mL for venlafaxine and 290 ng/mL for ODV; T_{max}'s were 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended-release capsule, the exposure to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower with the Effexor XR capsule. Effexor XR, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet.

Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg Effexor XR capsule.

Metabolism and Excretion

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. In vitro studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels ("poor metabolizers") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 ("extensive metabolizers"). The differences between the CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent.

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

Special Populations

Age and Gender: A population pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary (see **DOSAGE AND ADMINISTRATION**).

Extensive/Poor Metabolizers: Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, however, there is no need for different venlafaxine dosing regimens for these two groups.

Liver Disease: In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. Dosage adjustment is necessary in these patients (see **DOSAGE AND ADMINISTRATION**).

Renal Disease: In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR=10 to 70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR=10 to 70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56% compared to

normal subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these patients (see **DOSAGE AND ADMINISTRATION**).

Clinical Trials

Major Depressive Disorder

The efficacy of Effexor XR (venlafaxine hydrochloride) extended-release capsules as a treatment for major depressive disorder was established in two placebo-controlled, short-term, flexible-dose studies in adult outpatients meeting DSM-III-R or DSM-IV criteria for major depressive disorder.

A 12-week study utilizing Effexor XR doses in a range 75 to 150 mg/day (mean dose for completers was 136 mg/day) and an 8-week study utilizing Effexor XR doses in a range 75 to 225 mg/day (mean dose for completers was 177 mg/day) both demonstrated superiority of Effexor XR over placebo on the HAM-D total score, HAM-D Depressed Mood Item, the MADRS total score, the Clinical Global Impressions (CGI) Severity of Illness item, and the CGI Global Improvement item. In both studies, Effexor XR was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, and the retardation factor, as well as for the psychic anxiety score.

A 4-week study of inpatients meeting DSM-III-R criteria for major depressive disorder with melancholia utilizing Effexor (the immediate release form of venlafaxine) in a range of 150 to 375 mg/day (t.i.d. schedule) demonstrated superiority of Effexor over placebo. The mean dose in completers was 350 mg/day.

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

In one longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8-week open trial on Effexor XR (75, 150, or 225 mg, qAM) were randomized to continuation of their same Effexor XR dose or to placebo, for up to 26 weeks of observation for relapse. Response during the open phase was defined as a CGI Severity of Illness item score of ≤3 and a HAM-D-21 total score of ≤10 at the day 56 evaluation. Relapse during the double-blind phase was defined as follows: (1) a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness item score of ≥4 (moderately ill), (2) 2 consecutive CGI Severity of Illness item scores of ≥4, or (3) a final CGI Severity of Illness item score of ≥4 for any patient who withdrew from the study for any reason. Patients receiving continued Effexor XR treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

In a second longer-term trial, outpatients meeting DSM-III-R criteria for major depressive disorder, recurrent type, who had responded (HAM-D-21 total score ≤12 at the day 56 evaluation) and continued to be improved [defined as the following criteria being met for days 56 through 180: (1) no HAM-D-21 total score ≥20; (2) no more than 2 HAM-D-21 total scores >10, and (3) no single CGI Severity of Illness item score ≥4(moderately ill)] during an initial 26 weeks of treatment on Effexor (100 to 200 mg/day, on a b.i.d. schedule) were randomized to continuation of their same Effexor dose or to placebo. The follow-up period to observe patients for relapse, defined as a CGI Severity of Illness item score ≥4, was for up to 52 weeks. Patients

receiving continued Effexor treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

Generalized Anxiety Disorder

The efficacy of Effexor XR capsules as a treatment for Generalized Anxiety Disorder (GAD) was established in two 8-week, placebo-controlled, fixed-dose studies, one 6-month, placebo-controlled, fixed-dose study, and one 6-month, placebo-controlled, flexible-dose study in outpatients meeting DSM-IV criteria for GAD.

One 8-week study evaluating Effexor XR doses of 75, 150, and 225 mg/day, and placebo showed that the 225 mg/day dose was more effective than placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, both the HAM-A anxiety and tension items, and the Clinical Global Impressions (CGI) scale. While there was also evidence for superiority over placebo for the 75 and 150 mg/day doses, these doses were not as consistently effective as the highest dose. A second 8-week study evaluating Effexor XR doses of 75 and 150 mg/day and placebo showed that both doses were more effective than placebo on some of these same outcomes; however, the 75 mg/day dose was more consistently effective than the 150 mg/day dose. A dose-response relationship for effectiveness in GAD was not clearly established in the 75 to 225 mg/day dose range utilized in these two studies.

Two 6-month studies, one evaluating Effexor XR doses of 37.5, 75, and 150 mg/day and the other evaluating Effexor XR doses of 75 to 225 mg/day, showed that daily doses of 75 mg or higher were more effective than placebo on the HAM-A total, both the HAM-A anxiety and tension items, and the CGI scale during 6 months of treatment. While there was also evidence for superiority over placebo for the 37.5 mg/day dose, this dose was not as consistently effective as the higher doses.

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

Social Anxiety Disorder (Social Phobia)

The efficacy of Effexor XR capsules as a treatment for Social Anxiety Disorder (also known as Social Phobia) was established in two double-blind, parallel group, 12-week, multicenter, placebo-controlled, flexible-dose studies in adult outpatients meeting DSM-IV criteria for Social Anxiety Disorder. Patients received doses in a range of 75 to 225 mg/day. Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these two trials, Effexor XR was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

Examination of subsets of the population studied did not reveal any differential responsiveness on the basis of gender. There was insufficient information to determine the effect of age or race on outcome in these studies.

INDICATIONS AND USAGE

Major Depressive Disorder

Effexor XR (venlafaxine hydrochloride) extended-release capsules is indicated for the treatment of major depressive disorder.

The efficacy of Effexor XR in the treatment of major depressive disorder was established in 8- and 12-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (see **Clinical Trials**).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or the loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least five of the following nine symptoms during the same two-week period: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of Effexor (the immediate release form of venlafaxine) in the treatment of major depressive disorder in inpatients meeting diagnostic criteria for major depressive disorder with melancholia was established in a 4-week controlled trial (see **Clinical Trials**). The safety and efficacy of Effexor XR in hospitalized depressed patients have not been adequately studied.

The efficacy of Effexor XR in maintaining a response in major depressive disorder for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. The efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled trial (see **Clinical Trials**). Nevertheless, the physician who elects to use Effexor/Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Generalized Anxiety Disorder

Effexor XR is indicated for the treatment of Generalized Anxiety Disorder (GAD) as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of Effexor XR in the treatment of GAD was established in 8-week and 6-month placebo-controlled trials in outpatients diagnosed with GAD according to DSM-IV criteria (see **Clinical Trials**).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

Although the effectiveness of Effexor XR has been demonstrated in 6-month clinical trials in patients with GAD, the physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Social Anxiety Disorder

Effexor XR is indicated for the treatment of Social Anxiety Disorder, also known as Social Phobia, as defined in DSM-IV (300.23).

Social Anxiety Disorder (DSM-IV) is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is a marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of Effexor XR in the treatment of Social Anxiety Disorder was established in two 12-week placebo-controlled trials in adult outpatients with Social Anxiety Disorder (DSM-IV). Effexor XR has not been studied in children or adolescents with Social Anxiety Disorder (see **Clinical Trials**).

The effectiveness of Effexor XR in the long-term treatment of Social Anxiety Disorder, ie, for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**).

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine hydrochloride) extended-release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.

Clinical Worsening and Suicide Risk

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION, Discontinuing Effexor XR**, for a description of the risks of discontinuation of Effexor XR).

It should be noted that Effexor XR is not approved for use in treating any indications in the pediatric population.

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Effexor XR is not approved for use in treating bipolar depression.

Sustained Hypertension

Venlafaxine treatment is associated with sustained increases in blood pressure in some patients. Among patients treated with 75 to 375 mg/day of Effexor XR in premarketing studies in patients with major depressive disorder, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) $\geq$ 90 mm Hg and $\geq$ 10 mm Hg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 37.5 to 225 mg/day of Effexor XR in premarketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Among patients treated with 75 to 225 mg/day of Effexor XR in premarketing Social Anxiety Disorder studies, 1.4% (4/277) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3% to 7% at 100 to 300 mg/day to 13% at doses above 300 mg/day. An insufficient number

of patients received mean doses of Effexor XR over 300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

In placebo-controlled premarketing studies in patients with major depressive disorder with Effexor XR 75 to 225 mg/day, a final on-drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. In placebo-controlled premarketing GAD studies with Effexor XR 37.5 to 225 mg/day, up to 8 weeks or up to 6 months, a final on-drug mean increase in SDBP of 0.3 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.9 and 0.8 mm Hg, respectively, for placebo-treated patients. In placebo-controlled premarketing Social Anxiety Disorder studies with Effexor XR 75 to 225 mg/day up to 12 weeks, a final on-drug mean increase in SDBP of 1.3 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 1.3 mm Hg for placebo-treated patients.

In premarketing major depressive disorder studies, 0.7% (5/705) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 16 mm Hg, SDBP). In premarketing GAD studies up to 8 weeks and up to 6 months, 0.7% (10/1381) and 1.3% (7/535) of the Effexor XR-treated patients, respectively, discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 25 mm Hg, SDBP up to 8 weeks; 8 to 28 mm Hg up to 6 months). In premarketing Social Anxiety Disorder studies up to 12 weeks, 0.4% (1/277) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. In this patient, the blood pressure increase was modest (13 mm Hg, SDBP).

Sustained increases of SDBP could have adverse consequences. Therefore, it is recommended that patients receiving Effexor XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.

PRECAUTIONS

General

Discontinuation of Treatment with Effexor XR

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials in major depressive disorder. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

During marketing of Effexor XR, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Effexor XR. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION**).

Insomnia and Nervousness

Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with Effexor XR (venlafaxine hydrochloride) extended-release capsules than with placebo in pooled analyses of short-term major depressive disorder, GAD, and Social Anxiety Disorder studies, as shown in Table 1.

Table 1
Incidence of Insomnia and Nervousness in Placebo-Controlled Major Depressive Disorder, GAD, and Social Anxiety Disorder Trials

	Major Depressive Disorder		GAD		Social Anxiety Disorder	
Symptom	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274
Insomnia	17%	11%	15%	10%	23%	7%
Nervousness	10%	5%	6%	4%	11%	3%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Effexor XR in major depressive disorder studies.

In GAD trials, insomnia and nervousness led to drug discontinuation in 3% and 2%, respectively, of the patients treated with Effexor XR up to 8 weeks and 2% and 0.7%, respectively, of the patients treated with Effexor XR up to 6 months.

In Social Anxiety Disorder trials, insomnia and nervousness led to drug discontinuation in 3% and 0%, respectively, of the patients treated with Effexor XR up to 12 weeks.

Changes in Appetite and Weight

Treatment-emergent anorexia was more commonly reported for Effexor XR treated (8%) than placebo treated patients (4%) in the pool of short-term studies in major depressive disorder. Significant weight loss, especially in underweight depressed patients, may be an undesirable effect of Effexor XR treatment. A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in placebo-controlled major depressive

disorder trials. Discontinuation rates for anorexia and weight loss associated with Effexor XR were low (1.0% and 0.1%, respectively, of Effexor XR treated patients in major depressive disorder studies).

In the pool of GAD studies, treatment emergent anorexia was reported in 8% and 2% of patients receiving Effexor XR and placebo up to 8 weeks, respectively. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-treated and 1% of the placebo-treated patients up to 6 months in these trials. Discontinuation rates for anorexia and weight loss were low for patients receiving Effexor XR up to 8 weeks (0.9% and 0.3%, respectively).

In the pool of Social Anxiety Disorder studies, treatment emergent anorexia was reported in 20% and 2% of patients receiving Effexor XR and placebo up to 12 weeks, respectively. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-treated and 0.4% of the placebo-treated patients up to 12 weeks in these trials. Discontinuation rates for anorexia and weight loss were low for patients receiving Effexor XR up to 12 weeks (0.4% and 0.0%, respectively).

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products.

Activation of Mania/Hypomania

During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of Effexor XR-treated patients and 0.0% placebo patients. In premarketing GAD studies, 0.0% of Effexor XR-treated patients and 0.2% of placebo-treated patients experienced mania or hypomania. In premarketing Social Anxiety Disorder studies, no Effexor XR-treated patients and no placebo-treated patients experienced mania or hypomania. In all premarketing major depressive disorder trials with Effexor, mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with 0% of placebo patients. Mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs to treat major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Effexor XR should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example, volume-depleted, elderly, or taking diuretics.

Mydriasis

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Seizures

During premarketing experience, no seizures occurred among 705 Effexor XR-treated patients in the major depressive disorder studies, among 1381 Effexor XR-treated patients in GAD studies, or among 277 Effexor XR-treated patients in Social Anxiety Disorder studies. In all premarketing major depressive disorder trials with Effexor, seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Effexor XR, like many antidepressants, should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures.

Abnormal Bleeding

There have been reports of abnormal bleeding (most commonly ecchymosis) associated with venlafaxine treatment. While a causal relationship to venlafaxine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Serum Cholesterol Elevation

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see **ADVERSE REACTIONS-Laboratory Changes**). Measurement of serum cholesterol levels should be considered during long-term treatment.

Use in Patients With Concomitant Illness

Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering Effexor XR to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during venlafaxine's premarketing testing. The electrocardiograms were analyzed for 275 patients who received Effexor XR and 220 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials in major depressive disorder, for 610 patients who received Effexor XR and 298 patients who received placebo in 8-week double-blind, placebo-controlled trials in GAD, and for 195 patients who received Effexor XR and 228 patients who received placebo in 12-week double-blind, placebo-controlled trials in Social Anxiety Disorder. The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients in major depressive disorder studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for Effexor XR and decrease of 1.9 msec for placebo). The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients in the GAD studies did not differ significantly from that with placebo. The mean change from baseline in QTc for Effexor XR-treated patients in the Social Anxiety Disorder studies was increased relative to that for placebo-treated patients (increase of 2.8 msec for Effexor XR and decrease of 2.0 msec for placebo).

In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients in the major depressive disorder studies was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the GAD studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for Effexor XR and no change for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the Social Anxiety Disorder studies was significantly higher than that for placebo (a mean increase of 5 beats per minute for Effexor XR and no change for placebo).

In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, Effexor-treated patients had a mean increase in heart rate of 8.5 beats per minute compared with 1.7 beats per minute in the placebo group.

As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (eg, patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when using doses of Effexor above 200 mg/day.

Evaluation of the electrocardiograms for 769 patients who received immediate release Effexor in 4- to 6-week double-blind, placebo-controlled trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

In patients with renal impairment (GFR = 10 to 70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see **DOSAGE AND ADMINISTRATION**). Effexor XR, like all drugs effective in the treatment of major depressive disorder, should be used with caution in such patients.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Effexor XR (venlafaxine hydrochloride) extended-release capsules:

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Interference with Cognitive and Motor Performance

Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that venlafaxine therapy does not adversely affect their ability to engage in such activities.

Concomitant Medication
Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal preparations, since there is a potential for interactions.

Alcohol
Although venlafaxine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking venlafaxine.

Allergic Reactions
Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing
Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory Tests
There are no specific laboratory tests recommended.

Drug Interactions
As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Alcohol
A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or O-desmethylvenlafaxine (ODV) when venlafaxine was administered at 150 mg/day in 15 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

Cimetidine
Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, coadministration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than venlafaxine. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

Diazepam

Under steady-state conditions for venlafaxine administered at 150 mg/day, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam.

Haloperidol

Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

Lithium

The steady-state pharmacokinetics of venlafaxine administered at 150 mg/day were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. ODV also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium (see also *CNS-Active Drugs*, below).

Drugs Highly Bound to Plasma Proteins

Venlafaxine is not highly bound to plasma proteins; therefore, administration of Effexor XR to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Drugs that Inhibit Cytochrome P450 Isoenzymes

CYP2D6 Inhibitors: In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism of venlafaxine, reducing the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of the active metabolite. CYP2D6 inhibitors such as quinidine would be expected to do this, but the effect would be similar to what is seen in patients who are genetically CYP2D6 poor metabolizers (see *Metabolism and Excretion* under **CLINICAL PHARMACOLOGY**). Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

The concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied.

Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems.

Drugs Metabolized by Cytochrome P450 Isoenzymes

CYP2D6: In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

Imipramine - Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.

Risperidone - Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

CYP3A4: Venlafaxine did not inhibit CYP3A4 in vitro. This finding was confirmed in vivo by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

Indinavir - In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

CYP1A2: Venlafaxine did not inhibit CYP1A2 in vitro. This finding was confirmed in vivo by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

CYP2C9: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the pharmacokinetics of a single 500 mg dose of tolbutamide or the CYP2C9 mediated formation of 4-hydroxy-tolbutamide.

CYP2C19: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above).

Monoamine Oxidase Inhibitors

See **CONTRAINDICATIONS** and **WARNINGS.**

CNS-Active Drugs

The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated (except in the case of those CNS-active drugs noted above). Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required. Based on the mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is advised when venlafaxine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors (SRIs), or lithium.

Electroconvulsive Therapy

There are no clinical data establishing the benefit of electroconvulsive therapy combined with Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment.

Postmarketing Spontaneous Drug Interaction Reports

See **ADVERSE REACTIONS, Postmarketing Reports.**

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 1.7 times the maximum recommended human dose on a mg/m^2 basis. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma concentrations of venlafaxine at necropsy were 1 times (male rats) and 6 times (female rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenesis

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the in vitro BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the in vivo chromosomal aberration assay in rat bone marrow. ODV was not clastogenic in the in vitro Chinese hamster ovary cell chromosomal aberration assay, but elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow.

Impairment of Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose on a mg/m^2 basis.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 2.5 times (rat) or 4 times (rabbit) the maximum recommended human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects

Neonates exposed to Effexor XR, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **PRECAUTIONS-Drug Interactions-***CNS-Active Drugs*). When treating a pregnant woman with Effexor XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**).

Labor and Delivery

The effect of venlafaxine on labor and delivery in humans is unknown.

Nursing Mothers

Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. (See **WARNINGS-Clinical Worsening and Suicide Risk**).

Geriatric Use

Approximately 4% (14/357), 6% (77/1381), and 2% (6/277) of Effexor XR-treated patients in placebo-controlled premarketing major depressive disorder, GAD, and Social Anxiety Disorder trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase major depressive disorder studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older

individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly (see **CLINICAL PHARMACOLOGY**). No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information included in the **Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR** subsection is based on data from a pool of three 8- and 12-week controlled clinical trials in major depressive disorder (includes two U.S. trials and one European trial), on data up to 8 weeks from a pool of five controlled clinical trials in GAD with Effexor XR®, and on data up to 12 weeks from a pool of two controlled clinical trials in Social Anxiety Disorder. Information on additional adverse events associated with Effexor XR in the entire development program for the formulation and with Effexor (the immediate release formulation of venlafaxine) is included in the **Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR** subsection (see also **WARNINGS** and **PRECAUTIONS**).

Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR

Adverse Events Associated with Discontinuation of Treatment

Approximately 11% of the 357 patients who received Effexor® XR (venlafaxine hydrochloride) extended-release capsules in placebo-controlled clinical trials for major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 18% of the 1381 patients who received Effexor XR capsules in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 12% of the 555 placebo-treated patients in those studies. Approximately 17% of the 277 patients who received Effexor XR capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 274 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (ie, leading to discontinuation in at least 1% of the Effexor XR-treated patients at a rate at least twice that of placebo for either indication) are shown in Table 2.

Table 2
Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials[1]

Adverse Event	Percentage of Patients Discontinuing Due to Adverse Event					
	Major Depressive Disorder Indication[2]		GAD Indication[3,4]		Social Anxiety Disorder Indication	
	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274
Body as a Whole						
Asthenia	--	--	3%	<1%	1%	<1%
Headache	--	--	--	--	2%	<1%
Digestive System						
Nausea	4%	<1%	8%	<1%	4%	0%
Anorexia	1%	<1%	--	--	--	--
Dry Mouth	1%	0%	2%	<1%	--	--
Vomiting	--	--	1%	<1%	--	--
Nervous System						
Dizziness	2%	1%	--	--	2%	0%
Insomnia	1%	<1%	3%	<1%	3%	<1%
Somnolence	2%	<1%	3%	<1%	2%	<1%
Nervousness	--	--	2%	<1%	--	--
Tremor	--	--	1%	0%	--	--
Anxiety	--	--	--	--	1%	<1%
Skin						
Sweating	--	--	2%	<1%	1%	0%
Urogenital System						
Impotence[5]	--	--	--	--	3%	0%

[1] Two of the major depressive disorder studies were flexible dose and one was fixed dose. Four of the GAD studies were fixed dose and one was flexible dose. Both of the Social Anxiety Disorder studies were flexible dose.

[2] In U.S. placebo-controlled trials for major depressive disorder, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 192], % Placebo [n = 202]): hypertension (1%, <1%); diarrhea (1%, 0%); paresthesia (1%, 0%); tremor (1%, 0%); abnormal vision, mostly blurred vision (1%, 0%); and abnormal, mostly delayed, ejaculation (1%, 0%).

[3] In two short-term U.S. placebo-controlled trials for GAD, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 476]), % Placebo [n = 201]: headache (4%, <1%); vasodilatation (1%, 0%); anorexia (2%, <1%); dizziness (4%, 1%); thinking abnormal (1%, 0%); and abnormal vision (1%, 0%).

[4] In long-term placebo-controlled trials for GAD, the following was also a common event leading to discontinuation and was considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 535], % Placebo [n = 257]): decreased libido (1%, 0%).

[5] Incidence is based on the number of men (Effexor XR = 158, placebo = 153).

Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients

Tables 3, 4, and 5 enumerate the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of major depressive disorder (up to 12 weeks; dose range of 75 to 225 mg/day), of GAD (up to 8 weeks; dose range of 37.5 to 225 mg/day), and of Social Anxiety Disorder (up to 12 weeks; dose range of 75 to 225 mg/day), respectively, in 2% or more of patients treated with Effexor XR (venlafaxine hydrochloride) where the incidence in patients treated with Effexor XR was greater than the incidence for the respective placebo-treated patients. The table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Commonly Observed Adverse Events from Tables 3, 4, and 5:

Major Depressive Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the major depressive disorder (Table 3): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional events occurred in at least 5% of Effexor XR-treated patients (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning.

Generalized Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the GAD indication (Table 4): Abnormalities of sexual function (abnormal ejaculation and impotence), gastrointestinal complaints (nausea, dry mouth, anorexia, and constipation), problems of special senses (abnormal vision), and sweating.

Social Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for the 2 placebo-controlled trials for the Social Anxiety Disorder indication (Table 5): Asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.

Table 3
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Patients with Major Depressive Disorder[1,2]

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n = 357)	**Placebo** (n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Hypertension	4%	1%
Digestive System		
Nausea	31%	12%
Constipation	8%	5%
Anorexia	8%	4%
Vomiting	4%	2%
Flatulence	4%	3%
Metabolic/Nutritional		
Weight Loss	3%	0%
Nervous System		
Dizziness	20%	9%
Somnolence	17%	8%
Insomnia	17%	11%
Dry Mouth	12%	6%
Nervousness	10%	5%
Abnormal Dreams[4]	7%	2%
Tremor	5%	2%
Depression	3%	<1%
Paresthesia	3%	1%
Libido Decreased	3%	<1%
Agitation	3%	1%
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%
Special Senses		
Abnormal Vision[5]	4%	<1%

Body System Preferred Term	% Reporting Event Effexor XR (n = 357)	 Placebo (n = 285)
Urogenital System		
Abnormal Ejaculation (male)[6,7]	16%	<1%
Impotence[7]	4%	<1%
Anorgasmia (female)[8,9]	3%	<1%

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Effexor XR, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis, and sinusitis.
[2] <1% indicates an incidence greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[5] Mostly "blurred vision" and "difficulty focusing eyes."
[6] Mostly "delayed ejaculation."
[7] Incidence is based on the number of male patients.
[8] Mostly "delayed orgasm" or "anorgasmia."
[9] Incidence is based on the number of female patients.

Table 4
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in GAD Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 1381)	 Placebo (n = 555)
Body as a Whole		
Asthenia	12%	8%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Digestive System		
Nausea	35%	12%
Constipation	10%	4%
Anorexia	8%	2%
Vomiting	5%	3%

Body System Preferred Term	% Reporting Event Effexor XR (n = 1381)	 Placebo (n = 555)
Nervous System		
Dizziness	16%	11%
Dry Mouth	16%	6%
Insomnia	15%	10%
Somnolence	14%	8%
Nervousness	6%	4%
Libido Decreased	4%	2%
Tremor	4%	<1%
Abnormal Dreams[4]	3%	2%
Hypertonia	3%	2%
Paresthesia	2%	1%
Respiratory System		
Yawn	3%	<1%
Skin		
Sweating	10%	3%
Special Senses		
Abnormal Vision[5]	5%	<1%
Urogenital System		
Abnormal Ejaculation[6,7]	11%	<1%
Impotence[7]	5%	<1%
Orgasmic Dysfunction (female)[8,9]	2%	0%

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[5] Mostly "blurred vision" and "difficulty focusing eyes."
[6] Includes "delayed ejaculation" and "anorgasmia."
[7] Percentage based on the number of males (Effexor XR = 525, placebo = 220).
[8] Includes "delayed orgasm," "abnormal orgasm," and "anorgasmia."
[9] Percentage based on the number of females (Effexor XR = 856, placebo = 335).

Table 5
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients[1,2]

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n = 277)	**Placebo** (n = 274)
Body as a Whole		
Headache	34%	33%
Asthenia	17%	8%
Flu Syndrome	6%	5%
Accidental Injury	5%	3%
Abdominal Pain	4%	3%
Cardiovascular System		
Hypertension	5%	4%
Vasodilatation[3]	3%	1%
Palpitation	3%	1%
Digestive System		
Nausea	29%	9%
Anorexia[4]	20%	1%
Constipation	8%	4%
Diarrhea	6%	5%
Vomiting	3%	2%
Eructation	2%	0%
Metabolic/Nutritional		
Weight Loss	4%	0%
Nervous System		
Insomnia	23%	7%
Dry Mouth	17%	4%
Dizziness	16%	8%
Somnolence	16%	8%
Nervousness	11%	3%
Libido Decreased	9%	<1%
Anxiety	5%	3%
Agitation	4%	1%
Tremor	4%	<1%
Abnormal Dreams[5]	4%	<1%
Paresthesia	3%	<1%
Twitching	2%	0%
Respiratory System		
Yawn	5%	<1%
Sinusitis	2%	1%
Skin		
Sweating	13%	2%

Body System Preferred Term	% Reporting Event Effexor XR (n = 277)	 Placebo (n = 274)
Special Senses		
Abnormal Vision[6]	6%	3%
Urogenital System		
Abnormal Ejaculation[7,8]	16%	1%
Impotence[8]	10%	1%
Orgasmic Dysfunction[9,10]	8%	0%

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: back pain, depression, dysmenorrhea, dyspepsia, infection, myalgia, pain, pharyngitis, rash, rhinitis, and upper respiratory infection.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[6] Mostly "blurred vision."
[7] Includes "delayed ejaculation" and "anorgasmia."
[8] Percentage based on the number of males (Effexor XR = 158, placebo = 153).
[9] Includes "abnormal orgasm" and "anorgasmia."
[10] Percentage based on the number of females (Effexor XR = 119, placebo = 121).

Vital Sign Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled major depressive disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. Effexor XR treatment for up to 8 weeks in premarketing placebo-controlled GAD trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with less than 1 beat per minute for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 4 beats per minute, compared with an increase of 1 beat per minute for placebo. (See the **Sustained Hypertension** section of **WARNINGS** for effects on blood pressure.)

In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

Laboratory Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL compared with a mean final decrease of 7.4 mg/dL for placebo. Effexor XR treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dL and 2.3 mg/dL, respectively while placebo subjects experienced mean final decreases of

4.9 mg/dL and 7.7 mg/dL, respectively. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 11.4 mg/dL compared with a mean final decrease of 2.2 mg/dL for placebo.

Patients treated with Effexor tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL compared with a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see **PRECAUTIONS-General-***Serum Cholesterol Elevation*).

ECG Changes

In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo.

(See the *Use in Patients with Concomitant Illness* section of **PRECAUTIONS**).

Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR

During its premarketing assessment, multiple doses of Effexor XR were administered to 705 patients in Phase 3 major depressive disorder studies and Effexor was administered to 96 patients. During its premarketing assessment, multiple doses of Effexor XR were also administered to 1381 patients in Phase 3 GAD studies and 277 patients in Phase 3 Social Anxiety Disorder studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 2897 patients in Phase 2 to Phase 3 studies for major depressive disorder. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 5356 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 3, 4, and 5 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that,

although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: **frequent** adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients.

Body as a whole - **Frequent:** chest pain substernal, chills, fever, neck pain; **Infrequent:** face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; **Rare:** appendicitis, bacteremia, carcinoma, cellulitis.

Cardiovascular system - **Frequent:** migraine, postural hypotension, tachycardia; **Infrequent:** angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare:** aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor.

Digestive system - **Frequent:** increased appetite; **Infrequent:** bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; **Rare:** cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, periodontitis, proctitis, increased salivation, soft stools, tongue discoloration.

Endocrine system - **Rare:** goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.

Hemic and lymphatic system - **Frequent:** ecchymosis; **Infrequent:** anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; **Rare:** basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura.

Metabolic and nutritional - **Frequent:** edema, weight gain; **Infrequent:** alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, SGOT increased, SGPT increased, thirst; **Rare:** alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia.

Musculoskeletal system - **Frequent:** arthralgia; **Infrequent:** arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare:** pathological fracture, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture.

Nervous system - **Frequent:** amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; **Infrequent:** akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor; **Rare:** akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barre Syndrome, hyperchlorhydria, hypokinesia, impulse control difficulties, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis.

Respiratory system - **Frequent:** cough increased, dyspnea; **Infrequent:** asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; **Rare:** atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea.

Skin and appendages - **Frequent:** pruritus; **Infrequent:** acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare:** erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, petechial rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae.

Special senses - **Frequent:** abnormality of accommodation, mydriasis, taste perversion; **Infrequent:** cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** blepharitis, chromatopsia, conjunctival edema, deafness, exophthalmos, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis.

Urogenital system - **Frequent:** metrorrhagia,* prostatic disorder (prostatitis and enlarged prostate),* urination impaired, vaginitis*; **Infrequent:** albuminuria, amenorrhea,* cystitis, dysuria, hematuria, leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; **Rare:** abortion,* anuria, breast discharge, breast engorgement, balanitis,* breast enlargement, endometriosis,* female lactation,* fibrocystic breast, calcium crystalluria, cervicitis,* orchitis,* ovarian cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm,* vaginal dryness.*

*Based on the number of men and women as appropriate.

Postmarketing Reports

Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation,

supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsade de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Effexor XR (venlafaxine hydrochloride) extended-release capsules is not a controlled substance.

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Discontinuation effects have been reported in patients receiving venlafaxine (see **DOSAGE AND ADMINISTRATION**).

While venlafaxine has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Among the patients included in the premarketing evaluation of Effexor XR, there were 2 reports of acute overdosage with Effexor XR in major depressive disorder trials, either alone or in combination with other drugs. One patient took a combination of 6 g of Effexor XR and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.85 g of Effexor XR. This patient reported paresthesia of all four limbs but recovered without sequelae.

There were 2 reports of acute overdose with Effexor XR in GAD trials. One patient took a combination of 0.75 g of Effexor XR and 200 mg of paroxetine and 50 mg of zolpidem. This patient was described as being alert, able to communicate, and a little sleepy. This patient was hospitalized, treated with activated charcoal, and recovered without any untoward effects. The other patient took 1.2 g of Effexor XR. This patient recovered and no other specific problems were found. The patient had moderate dizziness, nausea, numb hands and feet, and hot-cold spells 5 days after the overdose. These symptoms resolved over the next week.

There were no reports of acute overdose with Effexor XR in Social Anxiety Disorder trials.

Among the patients included in the premarketing evaluation with Effexor, there were 14 reports of acute overdose with venlafaxine, either alone or in combination with other drugs and/or alcohol. The majority of the reports involved ingestion in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g, and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 µg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 µg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, and death have been reported.

Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference®* (*PDR*).

DOSAGE AND ADMINISTRATION

Effexor XR should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets.

Initial Treatment

Major Depressive Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of Effexor XR in moderately depressed outpatients, the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. While the relationship between dose and antidepressant response for Effexor XR has not been adequately explored, patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4. In the clinical trials establishing efficacy, upward titration was permitted at intervals of 2 weeks or more; the average doses were about 140 to 180 mg/day (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for Effexor (the immediate release form of venlafaxine), more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day). Whether or not higher doses of Effexor XR are needed for more severely depressed patients is unknown; however, the experience with Effexor XR doses higher than 225 mg/day is very limited. (See **PRECAUTIONS-General-***Use in Patients with Concomitant Illness.*)

Generalized Anxiety Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Effexor XR in outpatients with Generalized Anxiety Disorder (GAD), the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Although a dose-response relationship for effectiveness in GAD was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days. (See the *Use in Patients with Concomitant Illness* section of **PRECAUTIONS**.)

Social Anxiety Disorder (Social Phobia)

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Effexor XR in outpatients with Social Anxiety Disorder, the initial dose of Effexor XR was 75 mg/day and the maximum dose was 225 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Although a dose-response relationship for effectiveness in patients with Social Anxiety Disorder was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days. (See the *Use in Patients with Concomitant Illness* section of **PRECAUTIONS**).

Switching Patients from Effexor Tablets

Depressed patients who are currently being treated at a therapeutic dose with Effexor may be switched to Effexor XR at the nearest equivalent dose (mg/day), eg, 37.5 mg venlafaxine two-times-a-day to 75 mg Effexor XR once daily. However, individual dosage adjustments may be necessary.

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Effexor XR, other SNRIs, or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with Effexor XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Effexor XR in the third trimester.

Patients with Hepatic Impairment

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared with normal subjects (see **CLINICAL PHARMACOLOGY**), it is recommended that the starting dose be reduced by 50% in patients with moderate hepatic impairment. Because there was much individual variability in clearance between patients with cirrhosis, individualization of dosage may be desirable in some patients.

Patients with Renal Impairment

Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10 to 70 mL/min) compared with normal subjects (see **CLINICAL PHARMACOLOGY**), it is recommended that the total daily dose be reduced by 25% to 50%. In patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 50% and that the dose be withheld until the dialysis treatment is completed (4 hrs). Because there was much individual variability in clearance between patients with renal impairment, individualization of dosage may be desirable in some patients.

Elderly Patients

No dose adjustment is recommended for elderly patients solely on the basis of age. As with any drug for the treatment of major depressive disorder, Generalized Anxiety Disorder, or Social Anxiety Disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance Treatment

There is no body of evidence available from controlled trials to indicate how long patients with major depressive disorder, Generalized Anxiety Disorder, or Social Anxiety Disorder should be treated with Effexor XR.

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or Effexor for periods of up to 52 weeks on the same dose (100 to 200 mg/day, on a b.i.d. schedule) (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**). Based on these limited data, it is not known whether or not the dose of Effexor/Effexor XR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

In patients with Generalized Anxiety Disorder, Effexor XR has been shown to be effective in 6-month clinical trials. The need for continuing medication in patients with GAD who improve with Effexor XR treatment should be periodically reassessed.

In patients with Social Anxiety Disorder, there are no efficacy data beyond 12 weeks of treatment with Effexor XR. The need for continuing medication in patients with Social Anxiety Disorder who improve with Effexor XR treatment should be periodically reassessed.

Discontinuing Effexor XR

Symptoms associated with discontinuation of Effexor XR, other SNRIs, and SSRIs, have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. In clinical trials with Effexor XR, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. Individualization of tapering may be necessary.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED

Effexor® XR (venlafaxine hydrochloride) extended-release capsules are available as follows:

37.5 mg, grey cap/peach body with W and "Effexor XR" on the cap and "37.5" on the body.
NDC 0008-0837-01, bottle of 100 capsules.
NDC 0008-0837-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

75 mg, peach cap and body with W and "Effexor XR" on the cap and "75" on the body.
NDC 0008-0833-01, bottle of 100 capsules.
NDC 0008-0833-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

150 mg, dark orange cap and body with W and "Effexor XR" on the cap and "150" on the body.
NDC 0008-0836-01, bottle of 100 capsules.
NDC 0008-0836-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

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Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

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EXHIBIT L

EXHIBIT REDACTED IN ITS ENTIRETY